The Jocic Reaction and the Synthesis of Vitamin E

by

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Finally, thanks must go to family and friends for invaluable support. In particular Ellie Harlow, who was always there for me when needed.

Declaration

All of the work described in this thesis is original research carried out at the University of Warwick between October 2014 and April 2018. I declare that any material described which is not original has been identified and properly referenced. I certify that the material within this thesis has not been submitted for a degree at any other university.

Abstract

This thesis begins with an introduction to Vitamin E and the Jocic reaction. Chapter 1 provides a review of the biological activity of vitamin E and related compounds and the synthesis, both racemic and asymmetric, of vitamin E compounds. Also discussed in this chapter is the Jocic reaction and the synthesis of trichloromethyl alcohol compounds.

Chapter 2 describes the asymmetric total syntheses of both α- and β-tocopherol, where an *intramolecular* Jocic reaction was used to provide a high enantiomeric excess. Difficulties encountered during the synthesis, and how these were overcome, are detailed.

Chapter 3 describes the novel use of hydride as a nucleophile in the Jocic reaction with tertiary polychloromethyl alcohols. This one-carbon homologation procedure was improved by the use of dichloro- rather than trichloromethyl alcohols. The scope of the reaction, mechanisms and stereochemical implications are discussed.

Abbreviations

Å	Angstrom
aq.	Aqueous
BACE-1	β-Site amyloid precursor protein cleaving enzyme
$[Bar^{F}{}_{4}]^{-}$	Tetrakis[3,5-*bis*(trifluoromethyl)phenyl]borate
BINAP	2',2-*bis*(Diphenylphosphino)-1',1'-binaphthyl
Boc	*Tert*-butyloxycarbonyl
BOXAX	*Bis*(oxazolyl)-1,1'-binaphthyl
BTAC	Benzyltriethylammonium chloride
BuLi	Butyl lithium
Cat.	Catalytic
Cbz	Carboxybenzyl
CEHC	2'-Carboxyethyl-6-hydroxychromane
cod	Cyclooctadiene
CTAC	Cetyltrimethylammonium chloride
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	*N*,*N*-dimethylamino pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
DPPB	Diphenylphosphanyl benzoate
EC_{50}	Half maximal effective concentration

EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq.	Equivalent(s)
Fm	Fluorenylmethyl
GAD	Generalised anxiety disorder
hfc	3-(Heptafluoropropylhydroxymethylene)-(+)-camphorate
HOBt	Hydroxybenzotriazole
IBX	Iodoxybenzoic acid
IPA	2-Propanol
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
LDL	Low-density lipoprotein
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
mGluRs	Metabotropic glutamate receptors
µW	Microwave
m.p	Melting point
NaTCA	Sodium trichloroacetate
Nu	Nucleophile
PMP	*Para*-methoxyphenol
Red-Al ®	Sodium *bis*(2-methoxyethoxy)aluminium hydride
SAR	Structure activity relationship
TASF	*Tris*(dimethylamino)sulfonium difluorotrimethyl silicate
TBAOH	Tetra-*n*-butylammonium hydroxide
TBAF	Tetra-*n*-butylammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDMS	*Tert*-butyldimethylsilane
TBDPS	*Tert*-butyldiphenylsilane

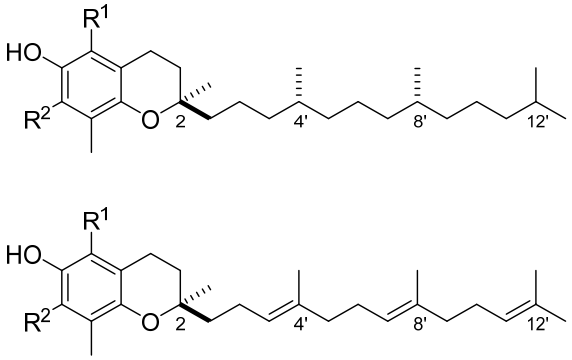
TCA	Trichloroacetic acid
TES	Triethylsilane
α-TEA	α-Tocopherol ether-linked acetic acid
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilane
TLC	Thin Layer Chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Tetramethylsilane
α-TOS	α-Tocopheryl succinate
Ts	Tosyl
α-TTP	α-Tocopherol transfer protein

Chapter 1: Introduction to Vitamin E and the Jocic Reaction

1.1 Discovery of Vitamin E

Vitamin E is the name given to a class of naturally occurring antioxidants consisting of eight different compounds. These eight compounds are divided into the tocopherols and the tocotrienols (Figure 1), which differ only in unsaturation of the phytyl side

chain. Depending on the extent and position of methylation around the aromatic ring these compounds are further designated α, β, γ or δ.



α-Tocopherol: R^1=Me, R^2=Me **1**
β-Tocopherol: R^1=Me, R^2=H **2**
γ-Tocopherol: R^1=H, R^2=Me **3**
δ-Tocopherol: R^1=H, R^2=H **4**

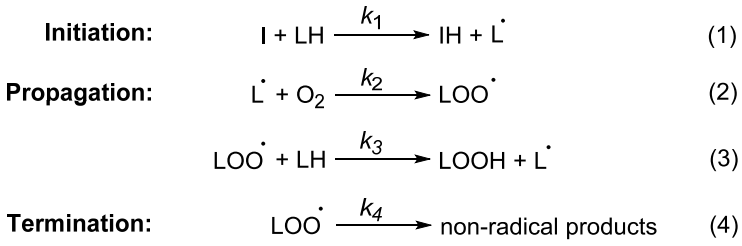
α-Tocotrienol: R^1=Me, R^2=Me **5**
β-Tocotrienol: R^1=Me, R^2=H **6**
γ-Tocotrienol: R^1=H, R^2=Me **7**
δ-Tocotrienol: R^1=H, R^2=H **8**

Figure 1. Naturally occurring vitamin E compounds.

In 1922, Evans and Bishop reported that rats which were fed an unnatural diet consisting mainly of milk, cornstarch and adequate vitamin A, B and C were infertile, and that fertility was restored by the feeding of lettuce leaves.[1] They had demonstrated that natural foods contained a substance essential for reproduction. Other groups reported the same results from similar experiments and the substance was first termed "Vitamin E" since vitamins A, B, C and D were already known.[2-4] Much of the early studies on the antioxidant activity of vitamin E were carried out by Mattill[5-10] and Evans.[11] Mattill and co-workers were one of the first groups to suggest that vitamin E acted as an antioxidant; they did this by measuring the uptake of oxygen from a variety of vegetable and animal fats and noted that uptake of oxygen was considerably slower in the presence of wheat germ oil (the best source of vitamin E at the time).[12, 13] Evans *et al.* isolated α-tocopherol in pure form from wheat germ oil in 1936[14] and shortly after its chemical structure was fully elucidated.[15] Olcott and Emerson then demonstrated the antioxidant activity of α, β and γ-tocopherols towards unsaturated fats definitively for the first time.[16]

1.2 Mechanism of Action

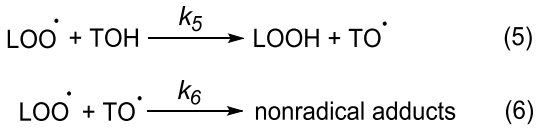
Lipid autoxidation (Scheme 1) is the process by which long chain fatty acids undergo oxidation under mild conditions, leading to rancidity.[17-19] In biological systems, the process is referred to as peroxidation and can result in the modification of low density lipoprotein (LDL)[20] and tissue damage.[21-23]



Scheme 1. Lipid autoxidation free radical chain reaction.

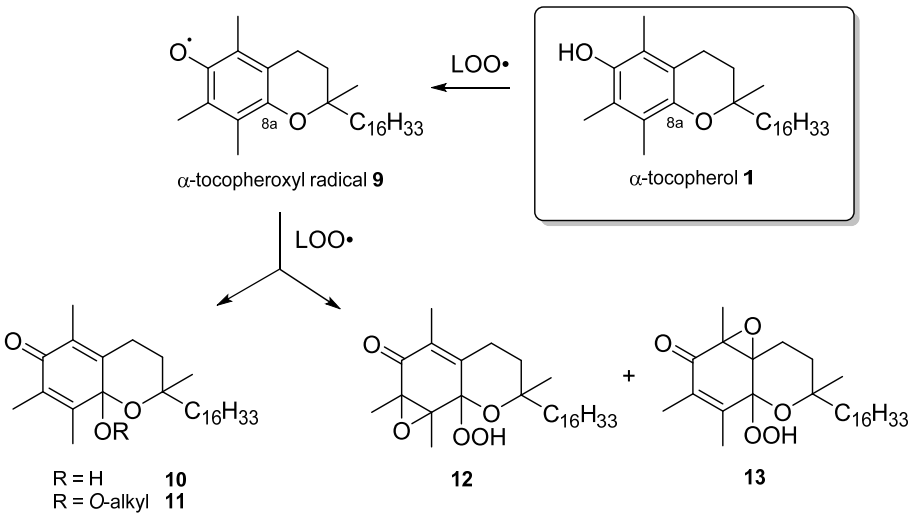
In order to measure the kinetics of lipid autoxidation using equations 1-4 (Scheme 1), the rate of initiation needs to be controlled and this is most commonly achieved using thermally-labile azo compounds as initiators.[24-26] Within biological systems initiators such as Fe^{+} ions,[27-30] organic hydroperoxides,[31-33] CCl_4[34, 35] and ethanol[36, 37] have all been described. The alkyl radicals (L•) generated are highly reactive and will react quickly with oxygen to form lipid peroxy radicals (LOO•), which react with further lipids to form lipid hydroperoxides (LOOH) and L• radicals which propagate the chain. Termination *via* dimerisation takes place when almost all of the lipids LH have been consumed.

Phenols are well known to act as inhibitors in radical chain reactions.[38-41] This is primarily due to their ability to donate a hydrogen atom to a propagating radical, thus terminating the chain. Therefore the antioxidant activity of vitamin E can be described by equations 5 and 6 (Scheme 2), where the phenol hydrogen atom (TOH) is donated to a lipid peroxy radical, forming a chromanoxyl radical (TO•).



Scheme 2. Inhibition of free radical propagation by tocopherols.

The chromanoxyl radical (TO•) will undergo radical-radical coupling to form adducts. Depending on whether the other radical is carbon-based or oxygen-based, the adduct will tend to be formed at the chromanoxyl oxygen[42] or at the 8a[43, 44] position respectively (Scheme 3).



Scheme 3. Reactions of α-tocopherol with peroxyl radicals.

The tocopherones **10-13** are then hydrolysed to the corresponding quinones by opening of the chromane ring. According to equations (5) and (6), one tocopherol molecule is therefore theoretically able to neutralise two lipid peroxy radicals.

1.3 Influence of Substituents on Activity

Vitamin E components have been the topic of a number of studies into antioxidant activity.[45-56] This antioxidant activity is primarily due to the ability of the tocopherols to terminate free radical chain reactions as discussed previously (Schemes 1 and 2). Therefore, in order to be an effective chain-breaking antioxidant the rate constant for

reaction (5) must be much greater than that for (3), $k_5 >> k_3$ (Schemes 1 and 2), which implies a high reactivity towards peroxy radicals. Howard and Ingold measured k_5 for a range of phenolic antioxidants with various substitution patterns, a selection of which are shown in Table 1.[41, 57]

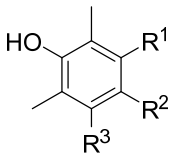
	R^1	R^2	R^3	$10^{-5}k_5$ ($M^{-1}s^{-1}$)
	H	OCH_3	H	94
	H	OCH_3	CH_3	130
	CH_3	OCH_3	CH_3	39
	CH_3	CH_3	CH_3	36
	CH_3	CH_3	H	11
	H	CH_3	H	8.5

Table 1. k_5 values for selected *o*-alkylated phenols at 30 °C.

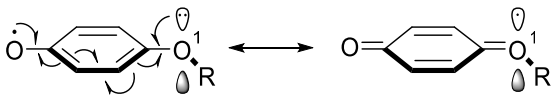
structure	$10^{-4}k_5$ ($M^{-1}s^{-1}$)	structure	$10^{-4}k_5$ ($M^{-1}s^{-1}$)
α-tocopherol	320	γ-tocopherol	140
β-tocopherol	130	δ-tocopherol	44

Table 2. k_5 values for the natural tocopherols at 30 °C.

They found that the greatest k_5 values were obtained with a *p*-methoxy substituent, and with three methyl groups in the other positions. From the data it was concluded that for simple phenols, k_5 is dependent both on the radical stabilising effect of groups in the *ortho* and *para* positions and on steric hindrance preventing the approach of the peroxy radical. For example, in the same study they found that 2,6-di-*tert*-butyl phenols were less reactive than the corresponding 2,6-dimethyl phenols due to the increased steric bulk of the *tert*-butyl group.

The k_5 values for the natural tocopherols were also measured under the same conditions and found to be in the order α > β ≈ γ > δ (Table 2), which has also been reported by others *in vitro*.[58] Due to their structural similarities it might be expected that *p*-methoxy-2,3,5,6-tetramethyl phenol should have a comparable antioxidant activity to α-tocopherol, but instead it was found that α-tocopherol was much more active. Given that there is no difference in steric hindrance in the positions *ortho* to the phenol group, the authors concluded that there must be a difference in the stability of the radicals formed.

If the group in the *para* position has lone pairs available these can overlap with the π system of the aromatic ring, which stabilises the phenoxyl radical by delocalisation (Scheme 4).



Scheme 4. Stabilisation of phenoxyl radicals by delocalisation.

In order for the lone pair electrons to overlap effectively they need to be perpendicular to the aromatic plane, and the extent of overlap will depend on the dihedral angle (θ) between the lone pair orbital on oxygen 1 and the *p* orbitals in the aromatic ring. Therefore a dihedral angle closer to 0 ° maximises the orbital overlap while an angle closer to 90 ° represents a minimum overlap. In *p*-methoxy-2,3,5,6-tetramethyl phenol the methoxy group can twist out of the plane in order to reduce steric clashing, resulting in a dihedral angle of 89 ° (Figure 2).[57, 59, 60] Orbital overlap is at a minimum and the oxygen lone pair is not able to stabilise the radical.

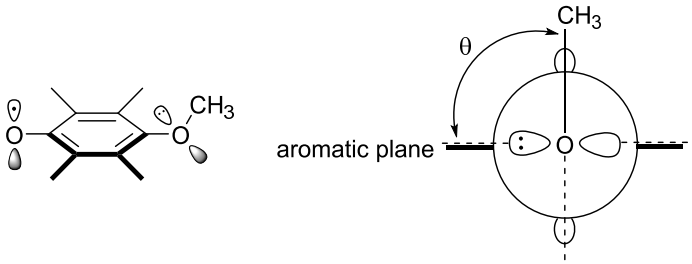


Figure 2. Newman projection of 4-methoxy-2,3,5,6-tetramethyl phenoxyl radical.

On the other hand, pentamethyl-6-hydroxy chromane is not able to twist out of the plane to the same extent due to its bicyclic nature, resulting in a dihedral angle of 17 ° and better orbital overlap (Figure 3).[57, 59, 60] Consequently, the chromane compound is able to stabilise the radical to a greater extent resulting in a larger k_5 value. This appears to be the fundamental reason for high vitamin E antioxidant activity compared to phenols which lack the fused ring system.

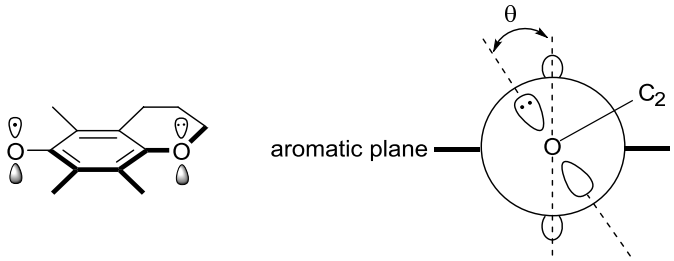
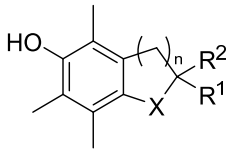


Figure 3. Newman projection of pentamethyl-6-hydroxy chromanoxyl radical.

Burton *et al*. investigated the effect of substitution on the chromane ring in an attempt to find a compound with greater antioxidant activity than α-tocopherol (Table 3).[61] An increase in k_5 was seen when the phytyl side chain was substituted for a CH_3 group, due to a decrease in puckering of the chromane ring resulting in a dihedral angle closer to 0 ° than in α-tocopherol. When $R^2 = CO_2H$ or CO_2CH_3 (compounds **15d** and **15e**) a decrease in activity is seen. The authors attribute this to an electron-withdrawing effect which reduces the ability of oxygen (X = O, Table 3) to donate its lone pair, consequently lowering the stability of the radical. Compound **15d** had previously been shown to be a more potent antioxidant than α-tocopherol in fats.[62, 63]



15a-i

compound	n	R^1	R^2	X	$10^{-4}\,k_5$ ($M^{-1}s^{-1}$)
a	2	CH_3	$C_{16}H_{33}$	O	324
b	2	CH_3	CH_3	O	377
c	2	H	H	O	267
d	2	CH_3	CO_2H	O	110
e	2	CH_3	CO_2CH_3	O	183
f	2	CH_3	CH_2CO_2H	O	187
g	2	H	H	$NC(O)CH_3$	12
h	2	H	H	NCH_2CH_3	197
i	1	H	CH_3	O	539

Table 3. The effect on k_5 of substitution around the chromane ring.

It might be expected that the compound with X = NCH_2CH_3 (tetrahydroquinoline, **15h**) should have higher activity than compounds with X = O due to the greater ability of nitrogen to stabilise neighbouring radical centres.[64, 65] However, a decrease in activity relative to α-tocopherol was measured. The reason for this is suggested to be that the *N*-ethyl group occupies the axial position in order to reduce steric clashing with the C-8 methyl group, preventing the nitrogen lone pair from overlapping with the π system (Figure 4).

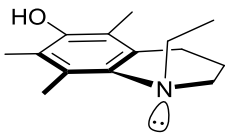


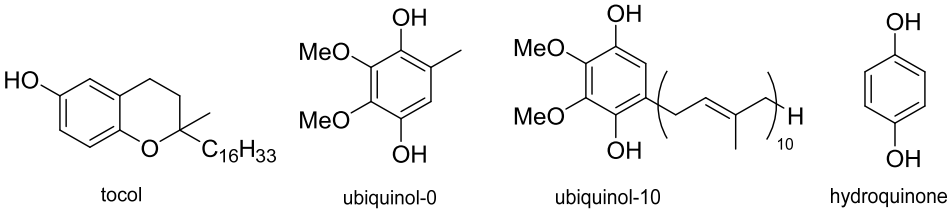
Figure 4. Presumed conformation of compound **15h**, with the nitrogen lone pair perpendicular to the π system.

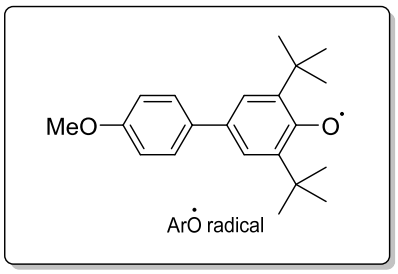
However, this conclusion was drawn from space-filling models as the authors were unable to grow crystals for X-ray crystallography. Compound **15i** with n = 1 (2,3-dihydrobenzofuran) showed the greatest k_5 value in the study, and this has been shown to be due to the small dihedral angle of 6 ° which increases radical stability as discussed previously.[57, 60] Other groups have carried out similar structure activity relationship (SAR) studies of this type.[66, 67]

Studies of the type by Burton *et al*. above are typically carried out by measuring the inhibited autoxidation of styrene in non-polar, organic solvent. Mukai *et al*. investigated the reaction of an ArO• radical with α-, β-, γ-, and δ-tocopherols, together with a selection of structurally related phenols, in a micellar solution designed to mimic cell membranes (Table 4).[58]

The data they obtained showed that the activity of the tocopherols is in the order α > β ≈ γ > δ in both micellar and ethanol solutions. The increase in rate constant seen in micellar solution is due to the lipophilicity of the compounds. They will be localised within the micelles and since the ArO• radicals are also lipid soluble, the reaction will take place inside the micelle. This close association is responsible for the large increase in rate. Tocol was shown to be around 90% less reactive towards radicals and this is due to a lack of electron donating groups *ortho* to the phenol.

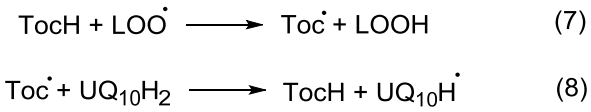
Ubiquinol-0 and ubiquinol-10 are known to act as lipid antioxidants in cell membranes.[68-70] The rate constant k_5 in micelles measured in this study was found to be comparable to vitamin E and a “regenerative” mechansim has been observed *in vitro*, whereby ubiquinol-10 donates an H atom to the Toc• radical (Scheme 5).[58, 71, 72] This type of synergistic relationship has been directly observed with ascorbic acid (vitamin C).[73-76]





	solvent	
antioxidant	**ethanol k_5 ($M^{-1}s^{-1}$)**	**micelle k_5 ($M^{-1}s^{-1}$)**
α-tocopherol	5.12 x 10^3	5.12 x 10^5
β-tocopherol	2.24 x 10^3	1.05 x 10^5
γ-tocopherol	2.42 x 10^3	1.00 x 10^5
δ-tocopherol	1.00 x 10^3	1.49 x 10^4
tocol	0.56 x 10^3	3.53 x 10^3
ubiquinol-10	4.70 x 10^3	1.25 x 10^5
ubiquinol-0	2.90 x 10^3	2.29 x 10^4
hydroquinone	3.35 x 10^2	2.68 x 10^3

Table 4. Measurement of k_5 values for vitamin E and related phenolic antioxidants at 25 °C, in both micellar (Triton X-100) and ethanol solution.



Scheme 5. Regeneration of tocopherol by $UQ_{10}H_2$ (Ubiquinol-10).

1.4 Comparison Between α-, β-, γ- and δ- forms

1.4.1 *In Vitro*

In vitro studies have shown α-tocopherol to be the most active form of vitamin E and δ-tocopherol to be the least active, with the β- and γ- forms in between.[50, 52, 57-59, 77] This must be primarily due to the greater extent of methylation of α-tocopherol around the aromatic ring, as discussed previously, since the dihedral angles imply a greater orbital overlap between the ring oxygen and the arene π system in γ- and δ-tocopherol.[78-80] In addition, a greater number of electron donating groups would be expected to stabilise a radical to a greater extent. However, studies of this type appear to be highly dependent on a number of experimental factors. For example, Cillard *et al*. studied the autoxidation of linoleic acid with and without tocopherols. They found that the antioxidant activities were in the reversed order, with δ-tocopherol most potent.[81] This has also been reported by other authors when measuring the relative antioxidant activities in fats.[82-84] Due to the reactive nature of radicals a number of side reactions can take place which may be dependent on the substrate being studied,[85, 86] temperature,[86] light,[86] concentration[87-89] or solvent.[90, 91] This wide range of variables may explain the contradictory nature of the reports in the literature and makes it difficult to compare results from different authors.

1.4.2 *In Vivo*

Whilst the relative antioxidant activities of the four tocopherols are all within an order of magnitude *in vitro*, in biological systems α-tocopherol is by far the most important antioxidant. Leth and Sondergaard used a rat resorption-gestation assay to determine the relative biological activities of the tocopherols (Table 5).[92] They found that δ-tocopherol had < 0.4% activity relative to so-called (all-*rac*)-α-tocopheryl acetate and similar results have been reported elsewhere in the literature.[93-97]

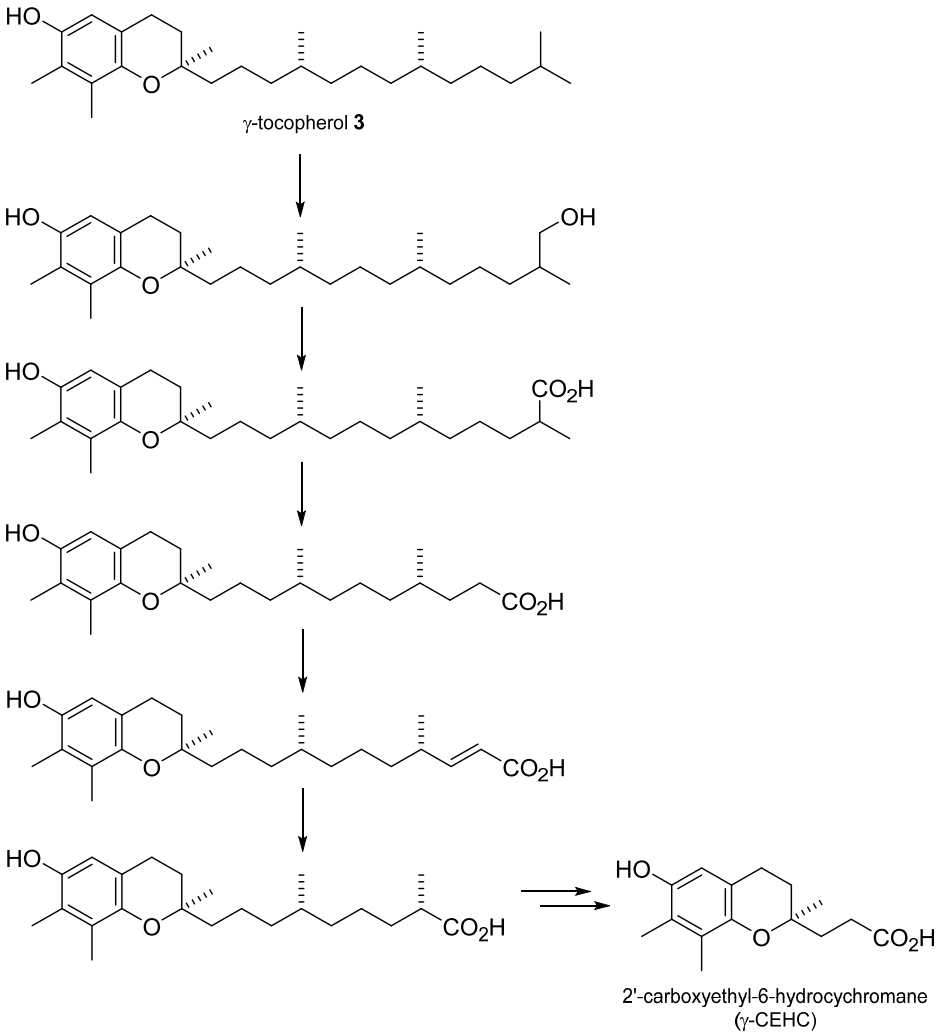
substrate	biological activity (%)[a]	α-TTP binding affinity (%)[b]
(*R*,*R*,*R*)-α-tocopherol	80	100
(*R*,*R*,*R*)-β-tocopherol	45	38.1 ± 9.3
(*R*,*R*,*R*)-γ-tocopherol	13	8.9 ± 0.6
(*R*,*R*,*R*)-δ-tocopherol	< 0.4	1.6 ± 0.3
(*R*,*R*,*R*)-α-tocopheryl acetate	-	1.7 ± 0.1
(*S*,*R*,*R*)-α-tocopherol	-	10.5 ± 0.4

Table 5. Comparison of natural tocopherols. [a] Relative to (2*RS*,4'*RS*,8'*RS*)-α-tocopheryl acetate (=100%). [b] Measured by calculating the relative IC_{50} values.

Given that this difference cannot be explained by the relative chemical reactivity of the tocopherols alone, other factors relating to their distribution, transport or bioavailability in cell tissues must be governing the measured relative activity. The most important factor appears to be recognition by the α-tocopherol transfer protein (α-TTP), which is the protein responsible for maintaining plasma α-tocopherol concentrations.[98-100]

Hosomi *et al*. measured the relative binding affinities for tocopherols and tocopherol analogues to α-TTP (Table 5).[101] They found that (*R*,*R*,*R*)-α-tocopherol displayed the highest binding affinity and δ-tocopherol displayed the lowest, which correlates well with the relative biological activities *in vivo*. In addition, they also studied the effect of stereochemistry on the binding affinity. From their results it can be seen that α-tocopherol with the (2*R*)-configuration has an almost 10-fold higher binding affinity to α-TTP than α-tocopherol with the (2*S*) configuration. Both of these results and similar studies by other groups[102-105] suggest that (*R*,*R*,*R*)-α-tocopherol is the optimal substrate for α-TTP and therefore it will be preferentially transported into cell membranes.

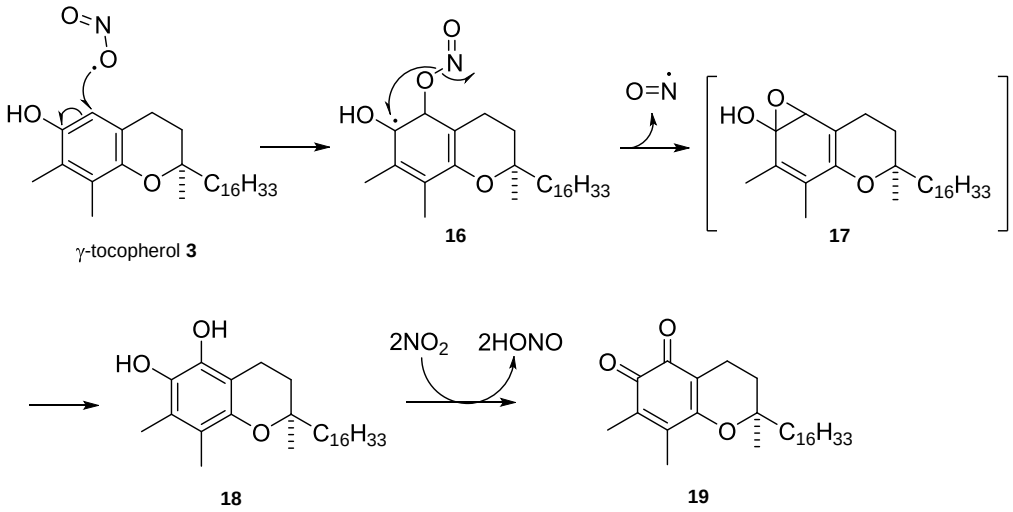
The metabolism of vitamin E provides an additional explanation for the differences in observed potency. It has been shown that the non-α-tocopherols are preferentially metabolised to the 2'-carboxyethyl-6-hydroxychromane (CEHC) forms by cytochrome P450s (Scheme 6).[106, 107]



Scheme 6. Pathway of metabolism of γ-tocopherol to its γ-CEHC form.

The fate of non-α-tocopherols is of importance given that the North American intake of γ-tocopherol exceeds that of α-tocopherol by a factor of 2-4.[108, 109] Soybean oil is thought to be the primary source of ingestion of vitamin E in the US diet, and this oil has been shown to contain 3-4 fold higher quantity of γ-tocopherol compared to α-tocopherol.[110] γ-Tocopherol may also have different reactivity due to the potentially nucleophilic C-5 site which is blocked in α-tocopherol. Cooney *et al.* showed that the

reaction of γ-tocopherol with low levels of NO_2 yielded 2,7,8 trimethyl-2-(4',8',12'-trimethyldecyl)-5-nitro 6-chromanol **16** and 2,7,8-trimethyl-2-(4',8',12'-trimethyltridecyl)-5,6-chromaquinone **19** (Scheme 7).[111, 112] Other groups have demonstrated the ability of γ-tocopherol to trap mutagenic electrophiles.[110, 113] It has also been suggested that γ-tocopherol may play a specific role in the prevention of heart disease and cancer.[114]



Scheme 7. Proposed mechanism for the trapping of NO_2 radicals by γ-tocopherol.

1.5 Vitamin E Deficiency in Humans

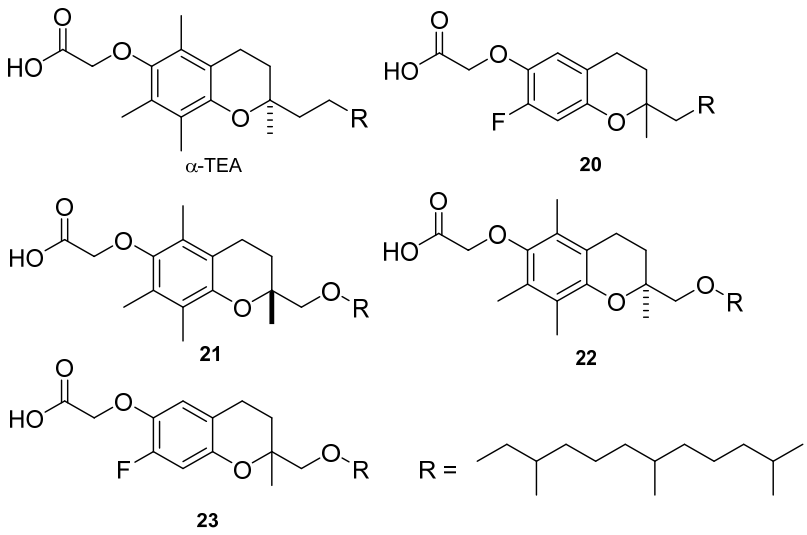
Patients with symptoms caused by vitamin E deficiency were first reported in the 1960s.[115, 116] This has been shown to be not due to lack of vitamin E in the diet, but due to either a defect in the gene for α-TTP,[117-120] or malabsorption of fatty acids,[121] resulting in a lack of α-tocopherol at cell membranes and therefore increased lipid peroxidation. An increased oxidative stress on tissue cells can result in neurodegenerative disease,[122] cardiovascular disease,[123] myopathy,[124, 125] or peripheral neuropathy.[126] The reason for this is attributed to a dying back of sensory nerves.[127]

1.6 Potential Non-antioxidant Applications

A number of roles not associated with antioxidant activity have been proposed for the tocopherols, including regulation of protein kinase C[128-130] and inhibition of cell proliferation.[131, 132] This conclusion was based largely on the fact that α-tocopherol had an effect on the signalling pathways whilst non-α forms did not. However, it has been suggested that these signalling pathways may in fact be dependent on the oxidative stress of the cell or tissue in question rather than being directly controlled by α-tocopherol.[133] Therefore, the apparent regulation of signalling pathways and other roles suggested for vitamin E may come back to its primary antioxidant function.

Vitamin E and analogues such as α-tocopheryl succinate (α-TOS) and α-tocopherol ether-linked acetic acid (α-TEA) have been shown to have potent anticancer properties in some cell types.[134-139] Chen *et al*. synthesised a number of related vitamin E analogues for anticancer functions (Table 6).[140] The data in table 6 shows that the highest anticancer activity was obtained with ether-linked analogues **21** and **22**. Chen *et al*. speculated that this may be due to the ether increasing the hydrophilicity of the compound and increasing uptake in the cells, but the mechanism is unknown.

Pharmaceutical compounds incorporate fluorine in order to increase bioavailability, lipophilicity or binding with a target protein.[141] It has also been shown that fewer methyl groups on the chromane head group may increase anticancer activity.[136] Therefore, the authors synthesised **20** and **23**, which are fluorinated at the C-7 position and unsubstituted at C-5 and C-8. These compounds were found to exhibit similar anticancer activity to α-TEA. However, given the considerable difference observed between the *in vitro* and *in vivo* antioxidant activity of the tocopherols due to their differing bioavailability, similar effects may be observed with anticancer activity. Therefore *in vivo* studies are potentially more useful.



cancer cell line	α-TEA	20	21	22	23
MDA-MB-231	35	34	16	18	27
MCF-7	31	60	29	21	35

Table 6. EC_{50} values (μM) for vitamin E analogues.

1.7 Tocotrienols

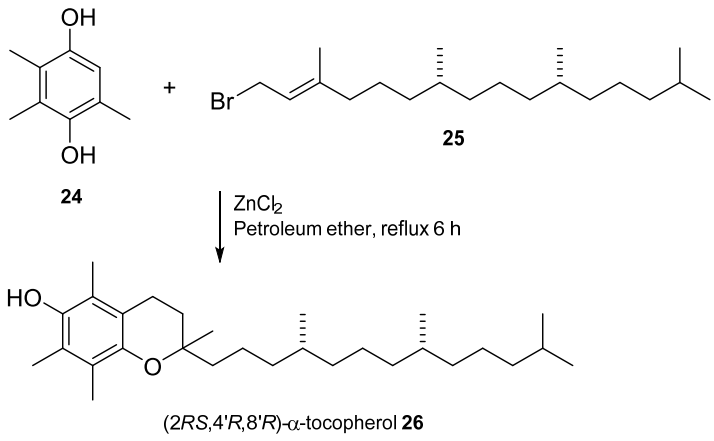
In comparison to the tocopherols, much less work has been done on the tocotrienols, which only differ in the phytyl side chain unsaturation (Figure 1). *In vivo* studies showed that α-tocotrienol has 30% of the biological activity of α-tocopherol and β-tocotrienol has only 5% of the activity of β-tocopherol, as determined by the rat resorption-gestation assay.[142] This can be attributed to discrimination by the α-TTP which specifically recognises a saturated phytyl chain.[143, 144] Consequently, the tocotrienol forms of vitamin E are not retained in tissues and membranes to the same extent as the tocopherols, resulting in lower biological activity.

Studies suggest that α-tocotrienol has a higher antioxidant activity than α-tocopherol *in vitro*.[145, 146] Suzuki *et al*. found α-tocotrienol to have greater reactivity towards peroxy radicals in membrane systems, whilst both tocopherol and tocotrienol forms

were identical in hexane solution.[147] Since the only structural difference between the two is in the side chain, this suggests that differing arrangements in the membrane could be affecting the reactivity. From their results Suzuki *et al*. suggested that α-tocotrienol is located closer to the membrane surface than α-tocopherol, allowing for greater interaction with peroxy radicals. However, work by Yoshida *et al*. yielded contrary results to those above, where they found very little difference in antioxidant activity between α-tocopherol and α-tocotrienol in membrane systems.[148]

1.8 Vitamin E Synthesis in Industry

(*R*,*R*,*R*)-α-Tocopherol is the most biologically relevant form of vitamin E due to its higher activity. However a mixture of all eight stereoisomers, so-called (all-*rac*)-α-tocopherol **26**, is the most important compound commercially. The first synthesis of α-tocopherol was reported by Karrer *et al*. in 1938, by the acid-catalysed condensation of trimethylhydroquinone **24** with phytyl bromide **25** (Scheme 8).[149, 150]

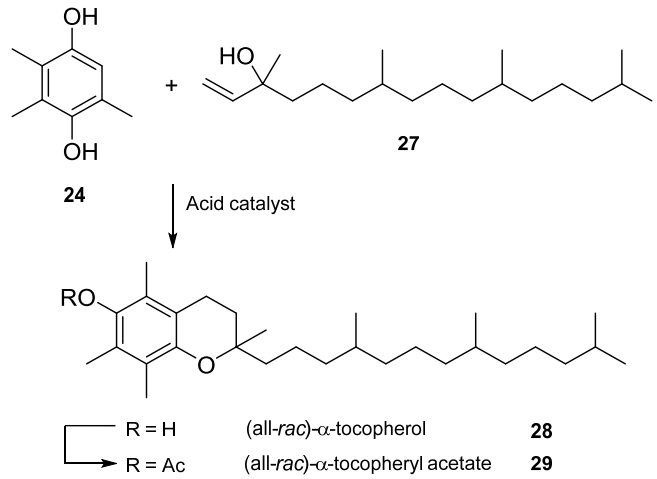


Scheme 8. First reported synthesis of α-tocopherol.

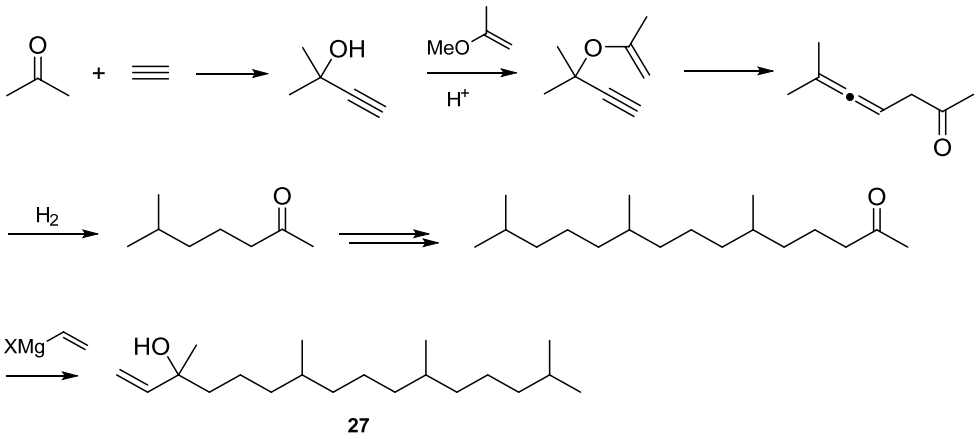
Note that phytyl bromide **25** was derived from natural (enantiomerically enriched) phytol, since this was the only available source of the compound at the time.

The current industrial-scale synthesis of (all-*rac*)-α-tocopherol and (all-*rac*)-α-tocopheryl acetate consists of the acid-catalysed condensation of

trimethylhydroquinone and (all-*rac*)-isophytol **27** (Scheme 9). Considerable effort has gone into the development of alternative catalysts to replace the conventional Lewis acids ($ZnCl_2$, $AlCl_3$, BF_3 among others), in order to increase selectivity and yield with a lower catalyst loading.[151-153] Trimethylhydroquinone is accessible on an industrial scale from mesitol, isophorones or diethyl ketone.[152, 154] (All-*rac*)-isophytol **27** is accessible using isoprenoid chemistry, in particular the acid-catalysed Carroll[155] and Saucy/Marbet[156] reactions for C_3 elongations. The starting materials are acetone, ethyne and hydrogen (Scheme 10).

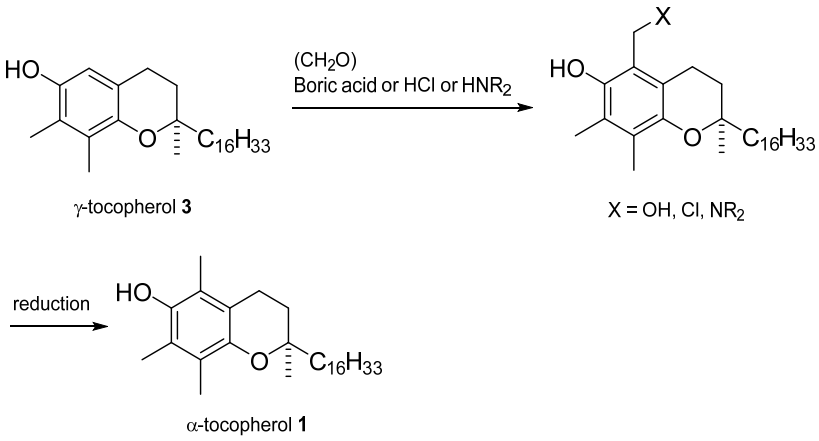


Scheme 9. Industrial synthesis of (all-*rac*)-α-tocopherol **28** and its acetate **29**.



Scheme 10. Industrial synthesis of (all-*rac*)-isophytol **27**.

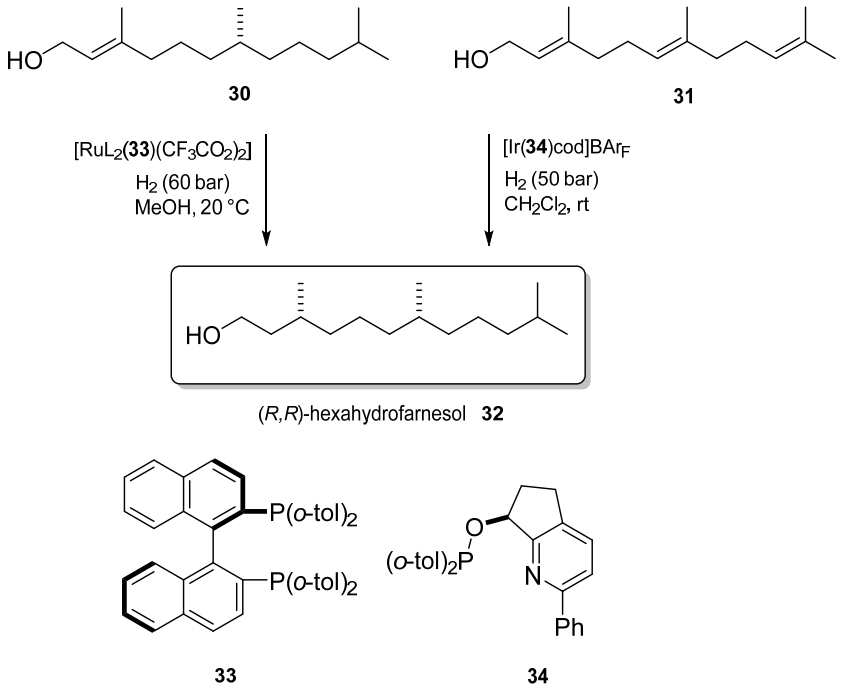
Given the increased biological activity of specifically (*R,R,R*)-α-tocopherol compared to the lower homologues and other stereoisomers, access to this compound on an industrial scale is important for pharmaceutical applications. Currently this is achieved by the processing of natural materials, such as soya beans and vegetable oil, which are rich in (*R,R,R*)-α-tocopherol. However, these materials also contain the lower homologues and so a "semi-synthetic" approach is used. All the tocopherols are first isolated by extraction, and then upgraded to the α-form using halo-,[157] amino-,[158] or hydroxy-[159] alkylation-reduction sequences (Scheme 11).



Scheme 11. Representative procedure for the upgrading of γ-tocopherol to α-tocopherol.

Netscher *et al*. have optimised procedures of this type using morpholine as the Mannich reagent in a variety of ratios with formaldehyde.[160] By adjusting the stoichiometry to 1:1-1.2 [δ-tocopherol:morpholine] they were also able to monoalkylate δ-tocopherol to the β- form, due to the higher reactivity of the C-5 position compared to the C-7 position. The reduction step is typically carried out using H_2 and Pd/C and the authors screened a considerable number of hydride reductants in an attempt to find alternative reagents. They found that $NaCNBH_3$ or $NaBH_4$/NaOH in *i*-BuOH were effective in the reduction of 5-(aminomethylated)-γ-tocopherol, but less effective when bis(aminomethylated)-δ-tocopherol was used as the substrate.

Relatively recent advances in catalytic asymmetric hydrogenation, based on the pioneering work of Noyori and co-workers, have allowed construction of the enantio- and diastereomerically enriched side-chain component **32** on an industrial scale (Scheme 12).

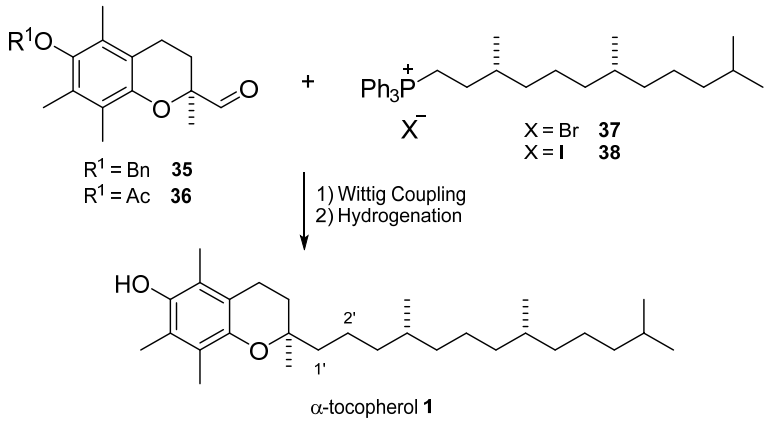


Scheme 12. Asymmetric hydrogenation of olefins using Ru and Ir catalysts.

Conditions developed by Noyori *et al.*[161, 162] were used at Roche to convert **30** into (*R*,*R*)-hexahydrofarnesol **32**, on a pilot scale with substrate:catalyst ratios of up to 150000:1.[163] Pfaltz *et al*. developed an Ir catalyst capable of the asymmetric hydrogenation of unfunctionalised, trialkyl substituted olefins with > 90% *d.e*. and > 99% *e.e*.[164, 165] In this way farnesol, **31**, was converted directly into (*R*,*R*)-hexahydrofarnesol **32**. One disadvantage of this route is that ligand **34** is not commercially available, unlike the BINAP derived ligands used for Noyori-type asymmetric hydrogenations.

1.9 α-Tocopherol Asymmetric Total Synthesis

The asymmetric total synthesis of (*R,R,R*)-α-tocopherol has been reported a number of times in the literature. Most of the syntheses to date can be categorised into: *1*) those which feature a C_1'-C_2' coupling; *2*) those which feature a stereospecific ring closing reaction; and *3*) those which feature a stereoselective ring closing reaction. The syntheses in category *1* are the most abundant and generally consist of the asymmetric construction of a chromane aldehyde (for example **35** or **36**), followed by a Wittig coupling with a side chain component (for example **37** or **38**, Scheme 13).

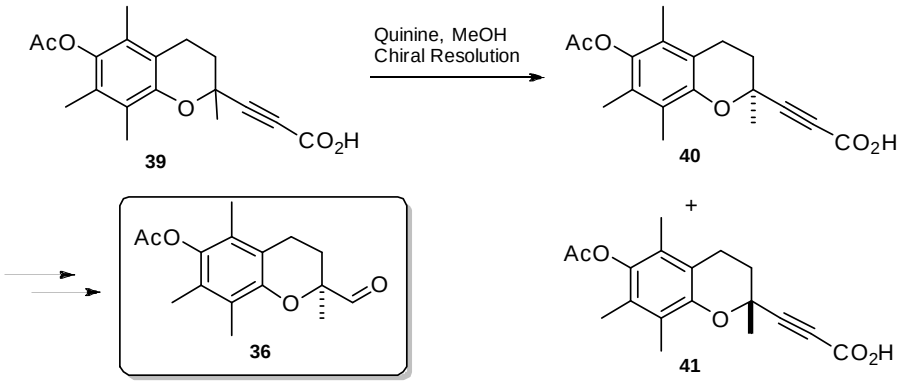


Scheme 13. C_1'-C_2' coupling route towards α-tocopherol.

Given the importance of the chromane moiety in vitamin E chemistry, some asymmetric approaches to their syntheses are also discussed below.

1.9.1 C_1'-C_2' Coupling Approach

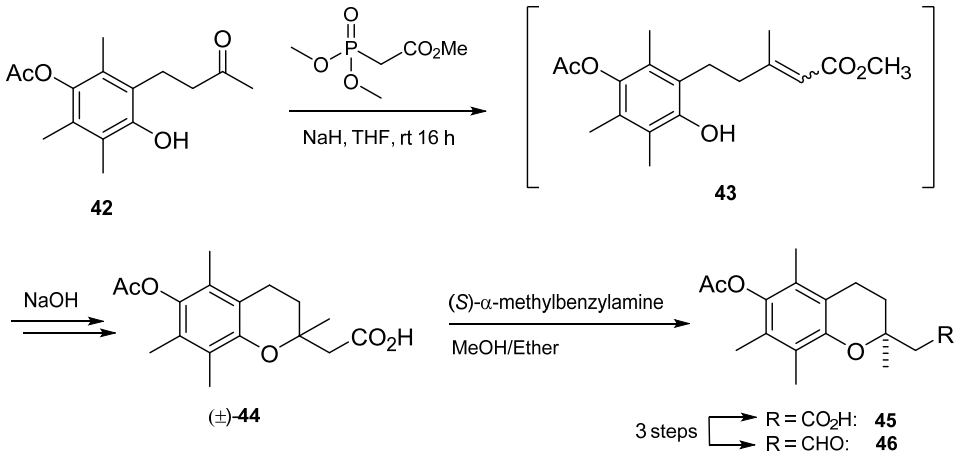
The first reported asymmetric total synthesis of α-tocopherol **1** was reported by Mayer *et al*. in 1963.[166] Their synthesis was the first example of the Wittig coupling method shown in Scheme 13. They used chiral resolution to obtain aldehyde **36 (**Scheme 14).



Scheme 14. Chiral resolution of racemic aldehyde (±)-**36**.

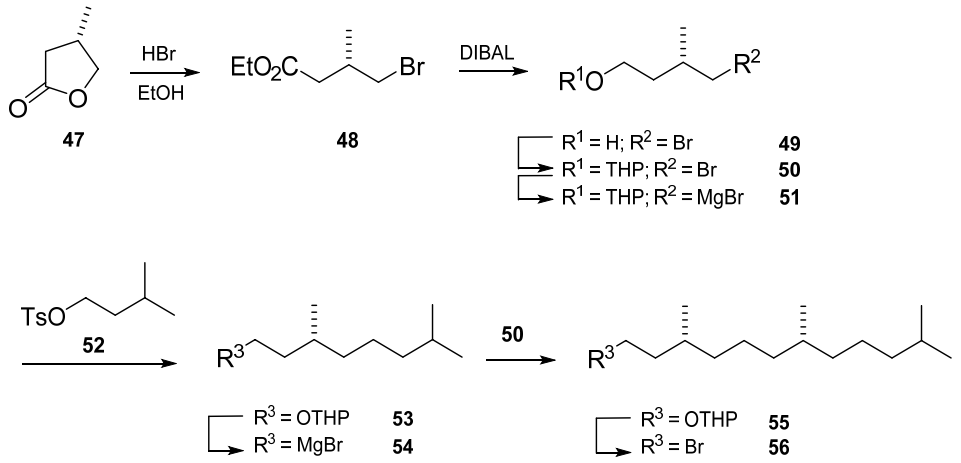
The authors were unable to resolve aldehyde (±)-**36** directly so it was converted into the carboxylic acid **39**, from which both enantiomers could be resolved using quinine. Conversion into the enantiomerically enriched aldehyde **36** from the desired enantiomer **40** was achieved over four steps; this compound was then subjected to a Wittig coupling with phosphonium bromide **37**, followed by hydrogenation over palladium to yield (*R,R,R*)-α-tocopherol.

Chiral resolutions of this type are common in the asymmetric syntheses of (*R,R,R*)-α-tocopherol. Scott *et al.* used chiral resolution to synthesise precursor aldehyde **46**, from which the synthesis was completed using a Wittig coupling (Scheme 15).[167] Construction of the chromane ring was achieved using a Wadsworth-Emmons reaction and hydrolysis of the resulting ester gave the acid (±)-**44**. Resolution with (*S*)-α-methylbenzylamine gave the enantiomerically enriched acid **45** in 34% yield. The side chain component was derived from natural phytol as the (*R,R*)-diastereoisomer.



Scheme 15. Synthesis of aldehyde **46** by chiral resolution.

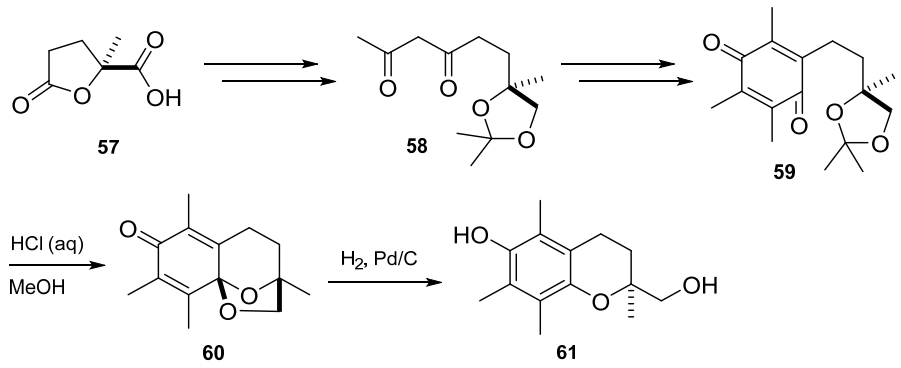
Schmid *et al*. demonstrated a synthetic route to the phytyl side chain component and used this in the total synthesis of α-tocopherol.[168, 169] This synthesis was based on the multiple Grignard coupling of chiral C_5 components, derived from the enantiomerically enriched lactone **47** (Scheme 16).[170]



Scheme 16. Synthesis of (3*R*,7*R*)-1-bromo-3,7,11-trimethyldodecane **56**. Some steps have been omitted for clarity.

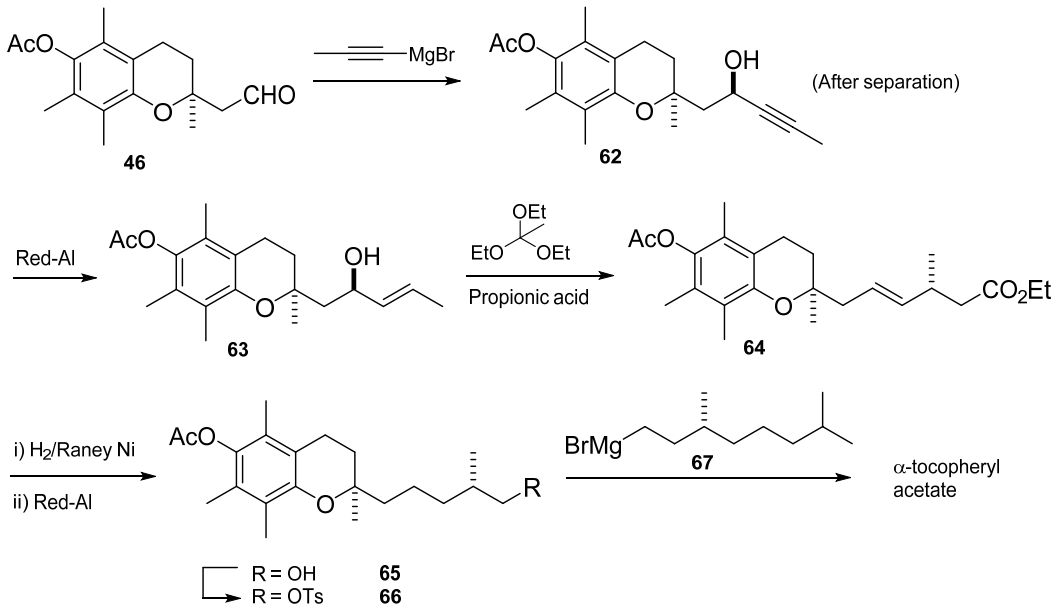
The bromide fragment **48** was obtained with an *e.e.* of > 97% based on ^{1}H NMR analysis with the chiral shift reagent Eu(hfc)$_3$. (3*R*,7*R*)-1-Bromo-3,7,11-trimethyldodecane **56** was synthesised in 11 linear steps with an overall yield of 36%, based on the lactone **47**. Completion of the synthesis of α-tocopherol was achieved using the method of Mayer *et al*.

A chiral γ-butyrolactone **57** was also used as a starting material in a synthesis by Cohen *et al*. (Scheme 17).[171] In this work the lactone **57** was elaborated into diketone **58** over a number of steps, followed by annulation and oxidation to generate the *p*-benzoquinone **59**. This compound was cyclised in aqueous HCl and methanol to yield the bridged ketal **60**, which could be reduced with H_2 and Pd/C to give the (*S*)-chroman-2-methanol **61.** None of the alternative seven-membered ring product was detected in the final reduction step, and only one enantiomer was observed by chiral shift ^{1}H NMR spectroscopy. Completion of the synthesis was carried out using the method of Mayer *et al*. to yield α-tocopherol in a total of 13 steps and with an overall yield of 6.5%.



Scheme 17. Synthesis of (*S*)-chroman-2-methanol **61**

An alternative approach was demonstrated by Chan *et al*. in which the side chain was built directly onto the chromane head group (Scheme 18).[172, 173] The key steps in this synthesis were a stereospecific Claisen rearrangement and a coupling with the enantiomerically enriched Grignard reagent **67**.



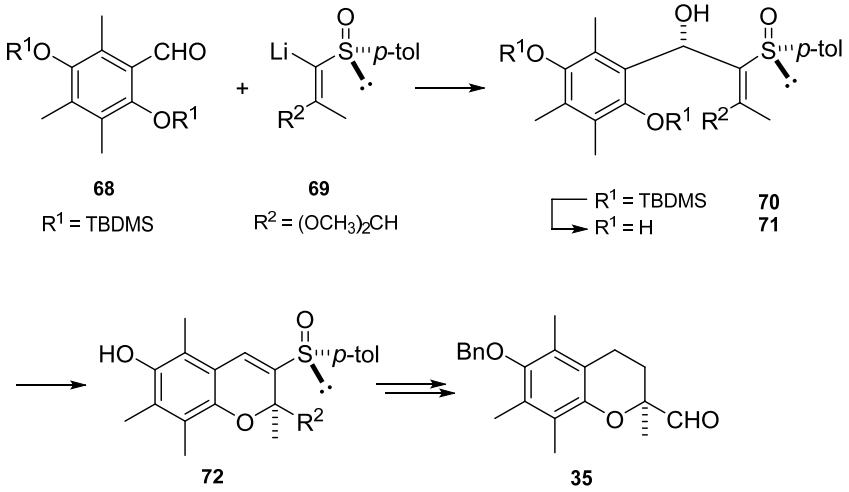
Scheme 18. Synthesis of α-tocopheryl acetate.

The chromane aldehyde **46** was prepared as described by Scott *et al.*[167] (Scheme 15). The required diastereomerically pure acetylenic carbinol **62** could be separated as a mixture of 3,5-dinitrobenzoates, followed by hydrolysis. Johnson-Claisen rearrangements are known to be highly stereoselective.[174] Treatment of allylic alcohol **63** with triethylorthoacetate and propionic acid at 140 °C yielded the (2*R*,4'*R*)-ester **64**, with an *e.e.* of 99%. Completion of the synthesis was achieved by the coupling of tosylate **66** with the enantiomerically enriched Grignard reagent **67**, analogous to the route of Schmid *et al.* (Scheme 16), in a total of ten linear steps (from aldehyde **46**) and an overall yield of 8.5%.

1.9.2 Other Approaches to Enantiomerically Enriched Chromanes

As can be seen above, the synthesis of enantiomerically enriched chromane structures commonly involves an optical resolution of a related racemic acid, often using chiral nitrogen bases such as quinine or (*S*)-α-methylbenzylamine. Enzymatic kinetic resolutions have also been shown to provide very high *e.e.* values.[175, 176] Asymmetric syntheses are less common. Solladie and Moine reported the use of an

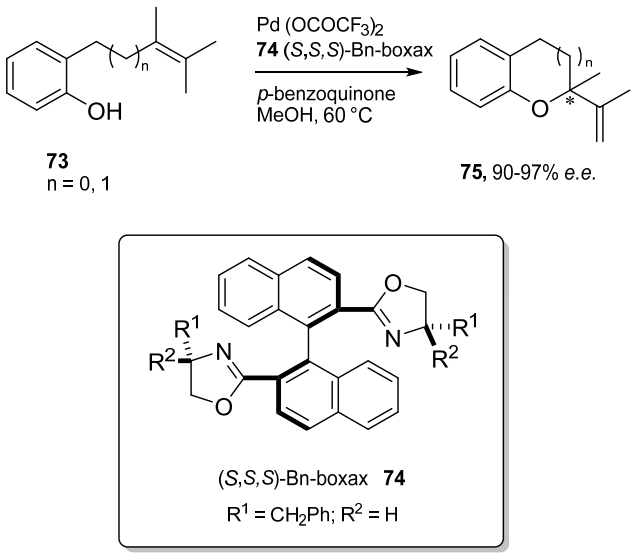
enantiomerically enriched sulfoxide in the synthesis of chromane aldehyde **35** (Scheme 19).[177]



Scheme 19. Synthesis of chromane aldehyde **35** *via* an enantiomerically enriched sulfoxide.

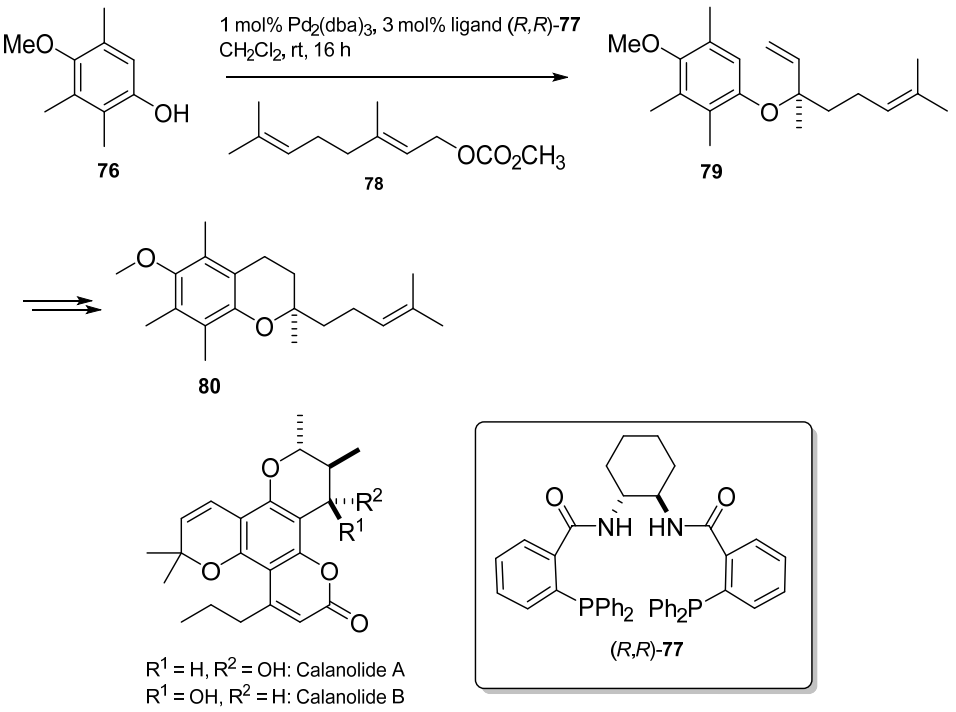
Vinyl sulfoxide **69** was prepared in six steps (34% yield), and its addition to aldehyde **68** at -78 °C provided the allylic alcohol as a single diastereoisomer. Heating in NaOMe/MeOH at reflux temperature furnished the chromene compound **72** by S_N2' ring closure, with no racemisation observed by ^1H NMR spectrometry using a chiral shift reagent. A further three steps (desulfurisation, benzylation and acetal hydrolysis) yielded (*S*)-aldehyde **35** in six steps from **68**, with an overall yield of 28%.

Uozumi *et al*. used palladium catalysis and a bisoxazoline (BOXAX) ligand to synthesise both chromane and dihydrobenzofuran structures with high *e.e.* (Scheme 20).[178] The reaction was tolerant of various substituents around the phenol ring with *e.e.* values of 90-97% obtained under the optimised conditions. The (*R*,*S*,*S*) diastereomer of the bisoxazoline ligand **74** gave poor selectivity (18% *e.e.*). Although a good *e.e.* of 97% was achieved for the chromane compound (n = 1), with the (*S*,*S*,*S*)-ligand, high catalyst loading (25 mol%) was required and 25% of unreacted starting material was recovered even under these conditions.



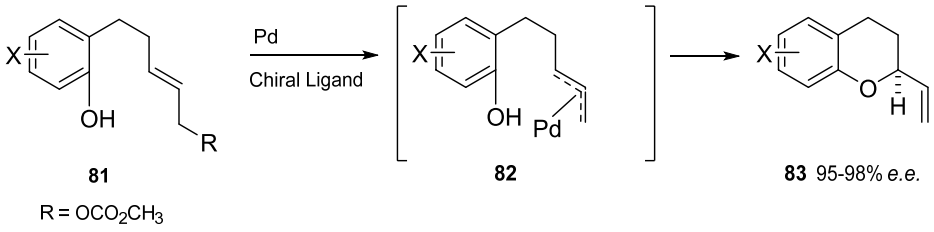
Scheme 20. Asymmetric Wacker-type cyclisation.

Trost *et al*. examined the asymmetric *O*-alkylation of phenols as a route towards the synthesis of Canolides A and B, and the chromane core of vitamin E (Scheme 21).[179] The aryl ether **79** was obtained with 98:2 regioselectivity and 77% *e.e.*, despite the tendency for phenols to attack the less hindered carbon in π-allylpalladium complexes.[180] Hydroboration of the double bond, followed by activation as the tosylate which underwent spontaneous intramolecular alkylation, yielded the chromane **80** in an overall yield of 42% over three steps.



Scheme 21. Chromane synthesis using an asymmetric *O*-alkylation.

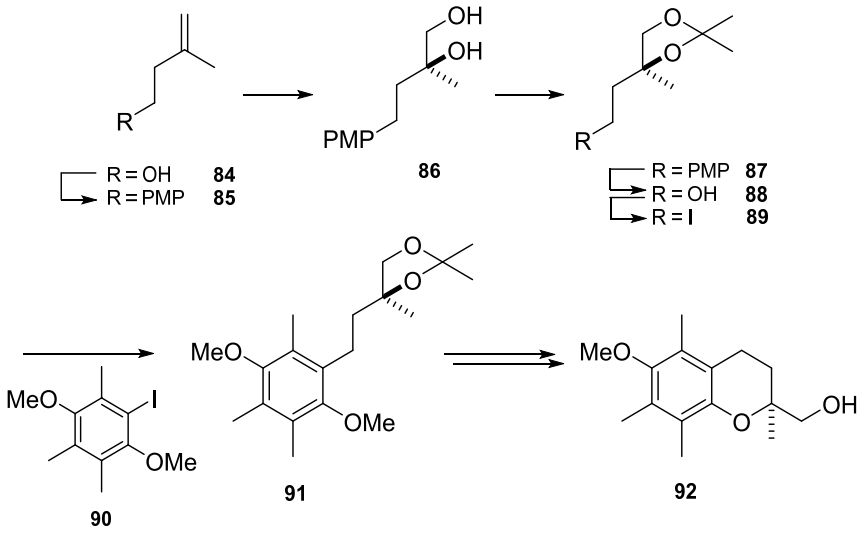
Trost *et al.* later improved on these moderate *e.e.* values by employing an *intramolecular* procedure (Scheme 22).[181, 182] Much improved *e.e.* values were obtained using this method and the issue of regioselectivity was also removed. This procedure also offered an improvement over similar work by Mizuguchi *et al.* and Labrosse *et al.* where only moderate *e.e.* values (up to 54%) were obtained.[183, 184]



Scheme 22. Intramolecular *O*-alkylation.

The leaving group was again chosen to be carbonate. Despite good *e.e.* values, the lengthy synthesis of the starting material **81** (13% over 11 steps) represents the biggest drawback to this procedure.

Tietze *et al.* used a Sharpless dihydroxylation and a palladium cross-coupling to synthesise the enantiomerically enriched chromane **92** (Scheme 23).[185, 186] Protection followed by dihydroxylation of the commercially available alcohol **84** provided diol **86** with an *e.e.* of 96%, and a yield of 93%. It was found that using a benzyl ether protecting group (R = Bn) gave a much lower *e.e.* of 53%. Conversion to the iodide **89** was achieved over three steps, followed by coupling to aryl iodide **90** using Zn/Cu/Pd system.



Scheme 23. Synthesis of chromanes using a Sharpless dihydroxylation.

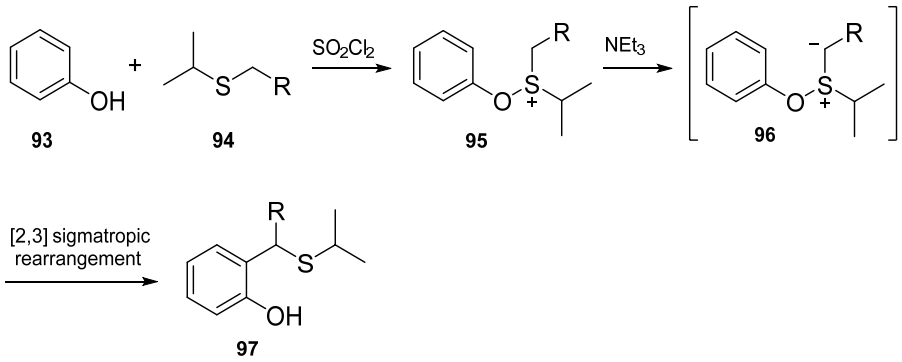
Conversion to the enantiomerically enriched chromane **92** from the acetonide **91** was previously reported.[171] This work represents a slight improvement on earlier work by Tietze *et al.* where the dihydroxylation of an enyne was used to generate the same precursor acetonide **91**, but with a lower *e.e.* of 84%.[187] Takabe *et al.* and Mizuguchi *et al.* also applied asymmetric epoxidations and dihydroxylations of this type in the synthesis of enantiomerically enriched chromanes.[188, 189]

1.9.3 Stereospecific Ring Closure Approach

The majority of the syntheses discussed up to this point have involved the C-C coupling of side chain components to an enantiomerically enriched chromane.

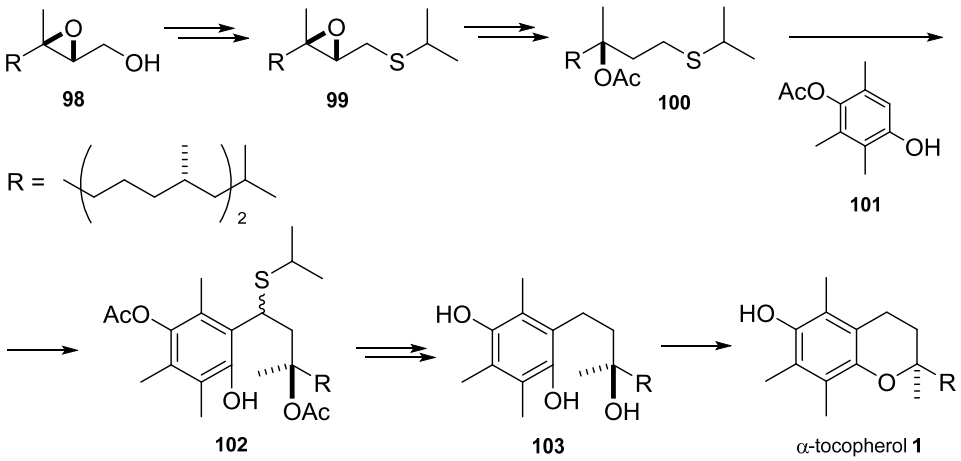
Another important approach to vitamin E synthesis is by a stereospecific ring closure, where the desired stereochemistry is defined beforehand.

Due to their high selectivity, asymmetric epoxidation and dihydroxylation reactions have seen considerable use in natural product synthesis.[190] Inoue *et al*. used a sulfoxide-mediated phenol alkylation and an asymmetric epoxidation in the total synthesis of α-tocopherol.[191] Phenoxy- and azasulfonium ylids such as **96** are known to undergo [2,3] sigmatropic rearrangements to yield *o*-alkylated products **97** (Scheme 24).[192-194]



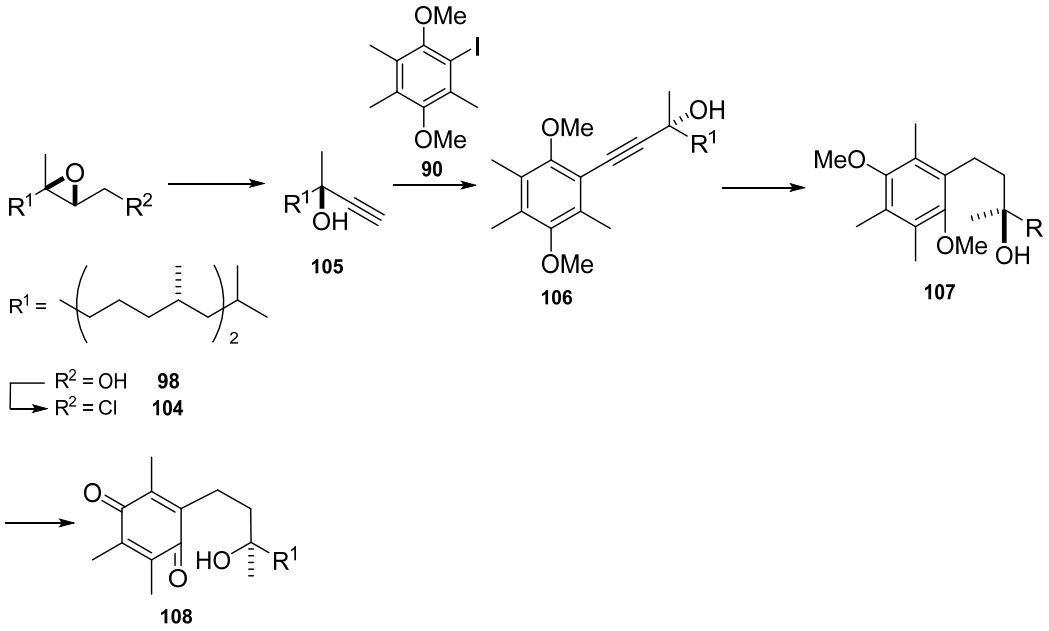
Scheme 24. *o*-Alkylation of phenols with dialkyl sulphides.

Scheme 25 shows the synthesis carried out by Inoue *et al*. Epoxide **98** was obtained in enantiomerically pure form by the Sharpless epoxidation[195] of the corresponding allylic alcohol, with the sulfide **100** generated over a further four transformations. Treatment of sulfide **100** with sulfuryl chloride, triethylamine and phenol **101** at -40 °C yielded the alkylated compound **102**. The synthesis was completed by desulfurisation, reduction of the acetyl groups and acid-catalysed cyclisation as described by Cohen *et al*.[196] The reported yield of α-tocopherol was 81% from sulfide **99**, with the *e.e.* at C-2 determined to be 96%.



Scheme 25. Total synthesis of α-tocopherol **1**.

Takano *et al*. reported the synthesis of α-tocopherol *via* an enantiomerically enriched 3-hydroxyacetylene (Scheme 26).[197]

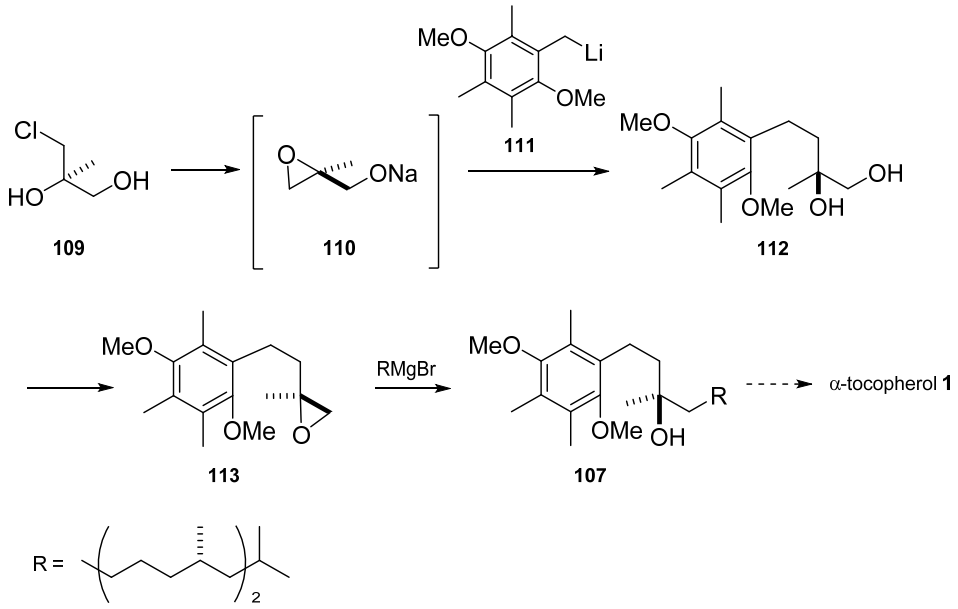


Scheme 26. Synthesis of known benzoquinone intermediate **108**.

The epoxide **98** was obtained from the Sharpless epoxidation of natural phytol. Takano *et al*. had previously shown that enantiomerically enriched chloroepoxides such as **104** could be converted into the corresponding 3-hydroxyacetylenes without racemisation.[198] Thus, treatment of epoxide **104** with *n*-butyllithium furnished the propargyl alcohol **105**. Cross-coupling with the aryl iodide **90** and subsequent

hydrogenation yielded alcohol **106**, which was converted into the known *p*-benzoquinone **108**. Completion of the synthesis from this compound was previously reported,[191] and α-tocopherol was obtained in nine steps and 24% overall yield from natural phytol.

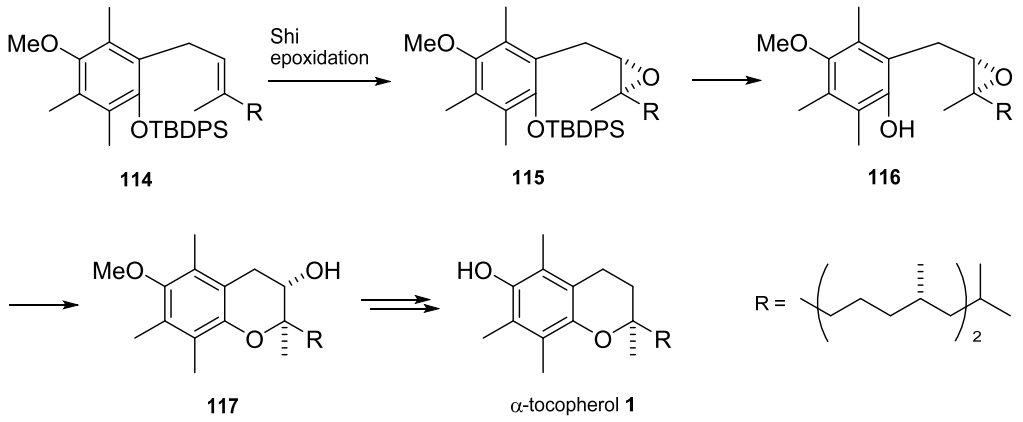
Hübscher and Barner reported the synthesis of α-tocopherol using several epoxide ring-opening reactions (Scheme 27).[199] Diol **109** was obtained by the initial Sharpless epoxidation of 2-methylprop-2-en-1-ol, in 81% overall yield over two steps and 98% *e.e.* Treatment with NaH and alkyllithium **111** yielded the diol **112**.



Scheme 27. Synthesis of α-tocopherol **1** by Hübscher and Barner.

Activation of the primary alcohol by tosylation allowed the formation of epoxide **113**, which was subsequently ring-opened by an enantiomerically enriched Grignard reagent. Completion of the synthesis from alcohol **107** was carried out using the method of Takano *et al.*,[197] to yield α-tocopherol **1** in an overall yield of 17% over eight steps (from 2-methylprop-2-en-1-ol).

Woggon *et al*. employed a similar approach, where an epoxide ring opening was used to directly synthesise the chromane ring (Scheme 28).[200]

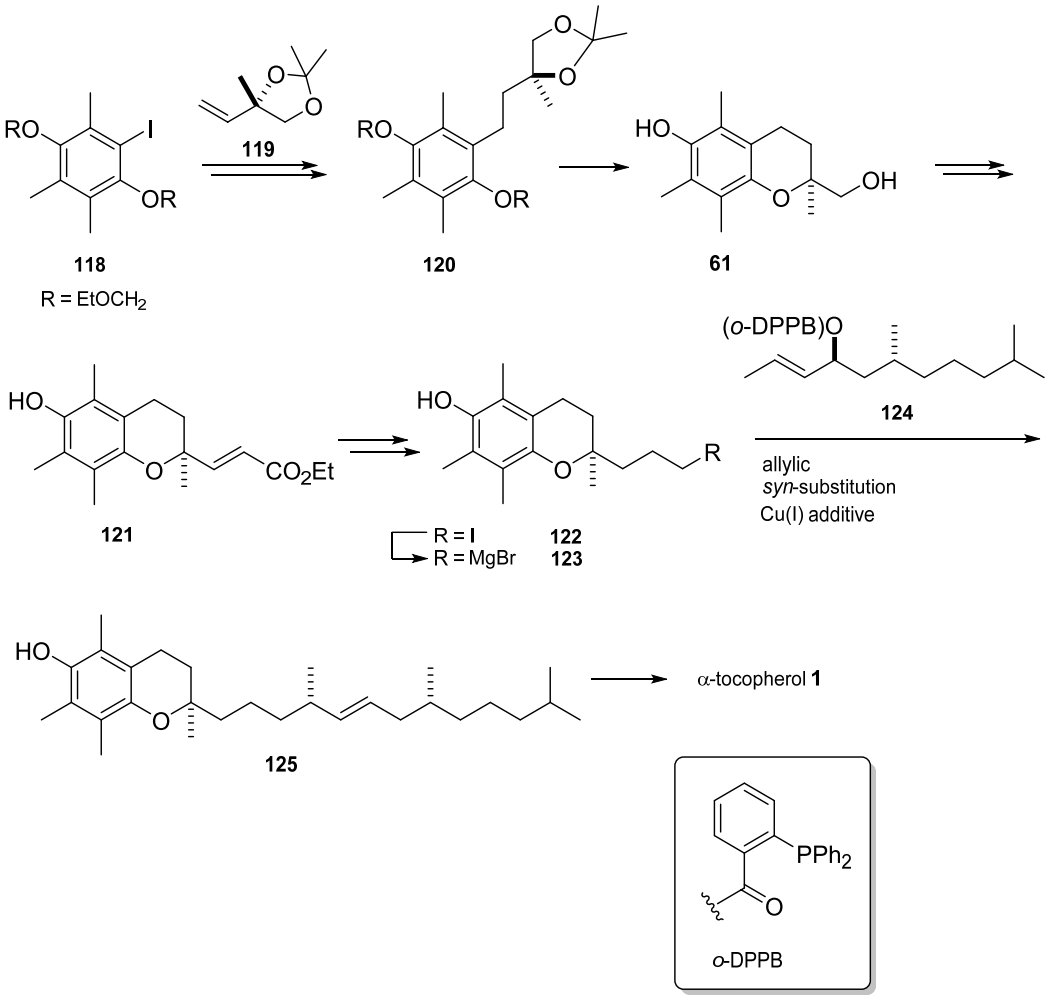


Scheme 28. Synthesis of α-tocopherol using a stereoselective Shi epoxidation.

Alkene **114** was synthesised from trimethylhydroquinone and phytyl bromide using a four step sequence. Shi epoxidation gave the epoxide **115** in a *d.e.* of 97%, where the bulky TBDPS (*tert*-butyldiphenylsilyl) protecting group was required to give good selectivity. Subsequent deprotection and cyclisation in 2M HCl/Et_2O gave the chromane **117** in 93% *d.e*. Note that the 6-*exo*-tet cyclisation is formally disfavoured according to Baldwin's rules, and the authors found that the 5-*exo*-tet benzofuran product was formed as a by-product in 19% yield. The slight decrease in *d.e*. is due to the extent of carbenium ion formation during the reaction. The chromane **117** was then converted into α-tocopherol, with an overall yield of 20% over 11 steps.

Rein *et al*. reported a synthesis where the key steps were construction of a chromane ring by stereospecific ring closure, and an *o*-DPPB (*o*-diphenylphosphanyl benzoate) -directed *syn* substitution (Scheme 29).[201] Synthesis of the chromane ring began with the coupling of aryl iodide **118** with alcohol **119**, derived from an enzymatic hydrolysis. Subsequent hydrogenation yielded the acetonide **120** from which the conversion into chromane **61** had been described by Cohen *et al*.[171, 196] A further six steps furnished the iodide precursor **122**. *o*-DPPB has been shown to act as a directing group in the addition of organic cuprates with excellent selectivity; furthermore, a single equivalent of organometallic reagent can be used in contrast to the two or more

equivalents commonly required.[202] Thus, the Grignard reagent **123** was coupled to alkene **124** in *syn* fashion. Hydrogenation furnished α-tocopherol in an overall yield of 30% over 13 steps. The coupling fragment **124** was synthesised in ten steps with an overall yield of 18%, where the stereochemistry was introduced by a rhodium-catalysed hydroformylation reaction, with a *d.e.* of 91%.

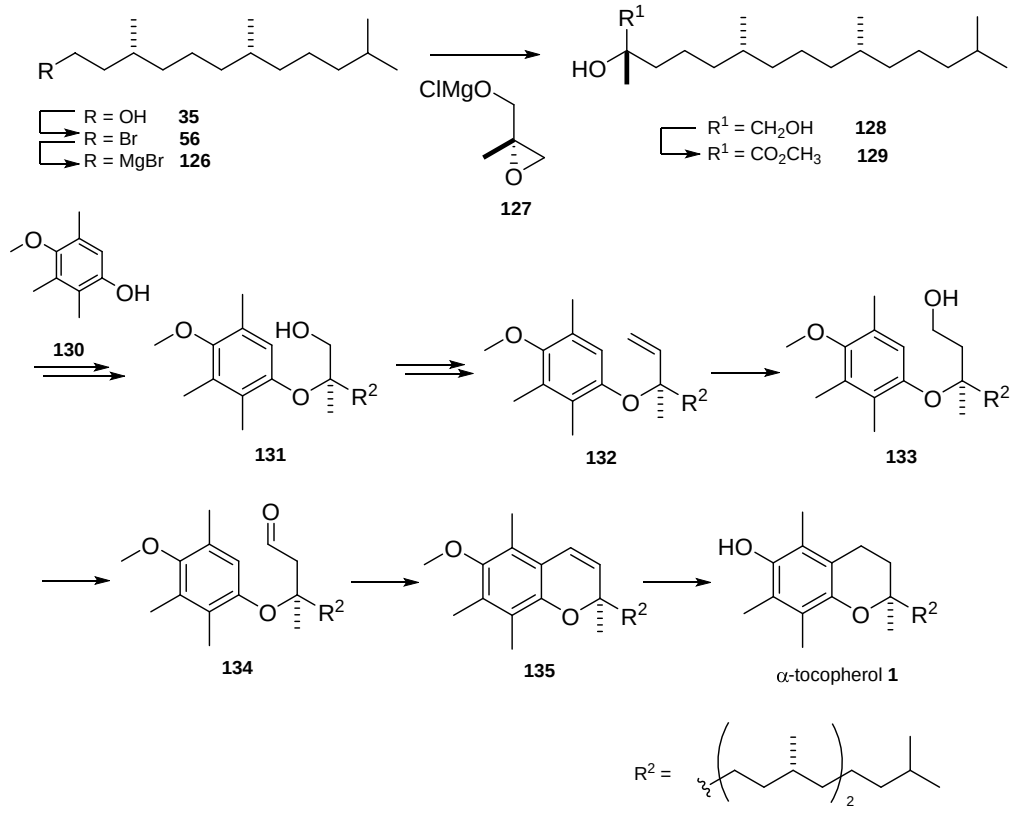


Scheme 29. α-Tocopherol synthesis using a directed cuprate addition.

Woggon *et al*. used the Mitsunobu reaction with an α-hydroxy ester to obtain the required stereochemistry at the C-2 position, and subsequent cyclisation yielded the chromane structure (Scheme 30).[203]

Epoxide **127** was prepared from the corresponding methylallyl alcohol by a Sharpless epoxidation protocol and treatment with EtMgCl. The key Mitsunobu reaction

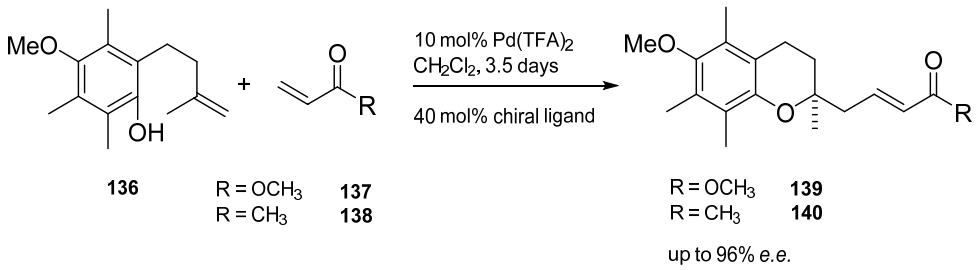
between monoprotected hydroquinone **130** and α-hydroxy ester **129** was achieved with 94% *d.e.* and complete inversion of configuration. Alcohol **133** was then obtained following olefination and rhodium-catalysed hydroboration. Oxidation to the aldehyde followed by acid-catalysed cyclisation yielded the chromene **135**, which after hydrogenation and demethylation yielded α-tocopherol **1** in a yield of 18% over 13 steps. The *d.e.* of the Mitsunobu reaction (94%) was retained throughout the synthesis.



Scheme 30. α-Tocopherol synthesis using a Mitsunobu reaction.

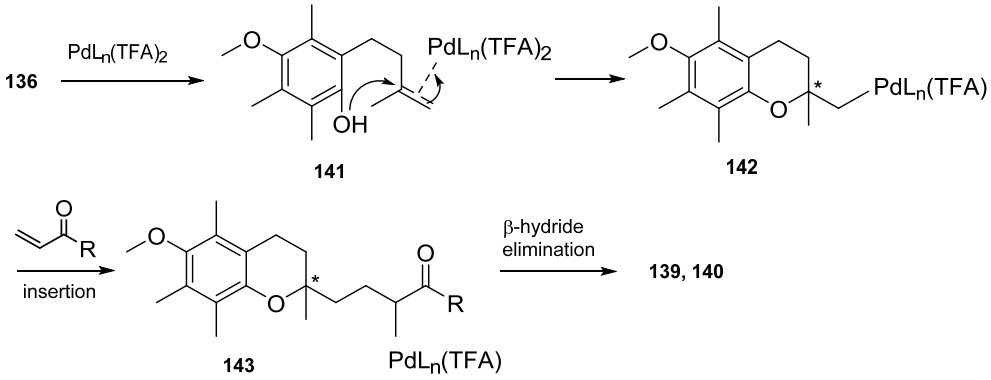
1.9.4 Stereoselective Ring Closure Approach

In contrast to the syntheses discussed above, approaches to the synthesis of tocopherols where the chromane ring system is constructed in *stereoselective* fashion are relatively scarce. Tietze *et al*. used a palladium-catalysed cyclisation to yield chromanes **139** and **140** with good enantioselectivity (Scheme 31).[204]



Scheme 31. Synthesis of chromanes *via* palladium-catalysed cyclisation.

A proposed mechanism is shown in scheme 32. The chirality is generated during the enantiofacial coordination of **136** to the palladium complex, where L_n = (*S*,*S*,*S*)-^{i}Pr-BOXAX.[205, 206]

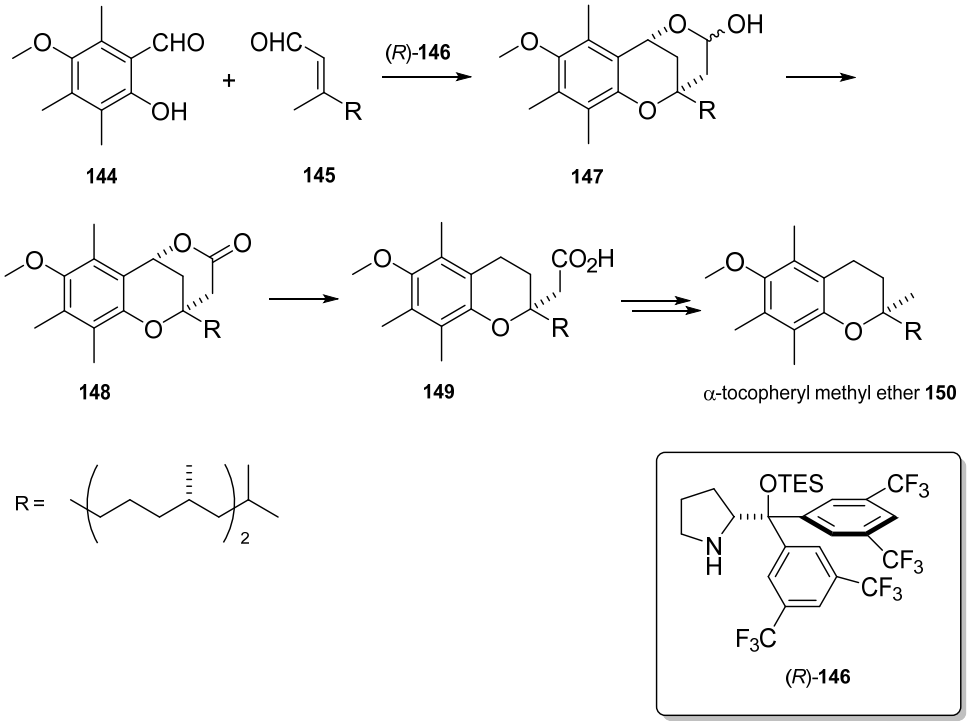


Scheme 32. Domino Wacker-type oxidation and Heck reaction.

Insertion of acrylate **137** gave the chromane **139** in 84% yield and with an *e.e.* of 96%; however, when R = CH_3 (**138**) the yield and *e.e.* of chromane **140** were 54% and 84% respectively. Dihydroxylation of the unsaturated ester **139** followed by oxidative cleavage with sodium periodate gave an aldehyde which could be converted into α-tocopherol **1** by known methods.[173]

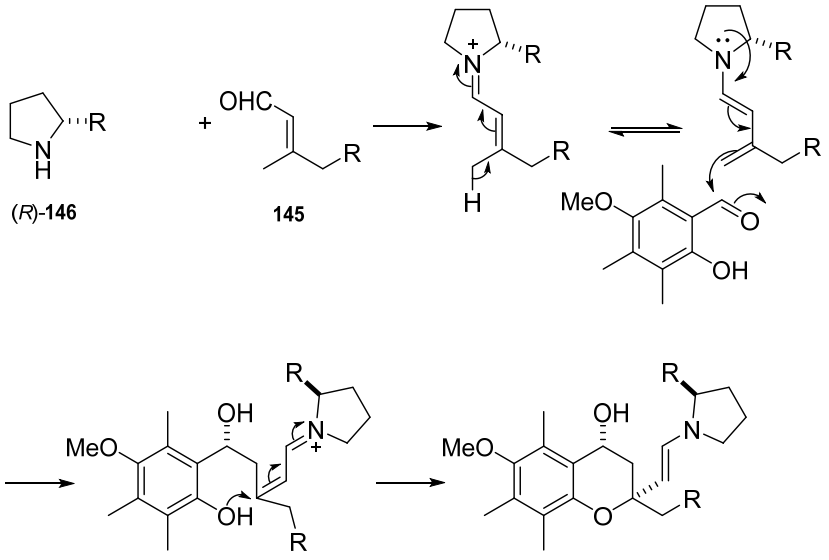
Woggon *et al.* employed a diastereoselective aldol/oxa-Michael addition reaction as the key step in the total synthesis of both (2*R*,4'*R*,8'*R*)-α-tocopherol and (2*S*,4'*R*,8'*R*)-α-tocopherol (Scheme 33).[207] Diarylprolinol-derived catalysts are known to provide good selectivity in a variety of addition reactions.[208-211] Therefore, the reaction between aldehydes **144** and **145**, derived from trimethylhydroquinone and natural

phytol respectively, gave hemiacetal **147** in 58% yield and 97% *d.e*. A proposed mechanism is shown in scheme 34. A number of proline derivatives were screened and (*R*)/(*S*)-**146** was found to give the best selectivity under the optimised conditions, although a fairly high catalyst loading (30 mol%) was required. The lactone **148** was readily hydrogenated to the carboxylic acid **149**, which could be converted into α-tocopheryl methyl ether **150** using a Barton decarboxylation.[212]



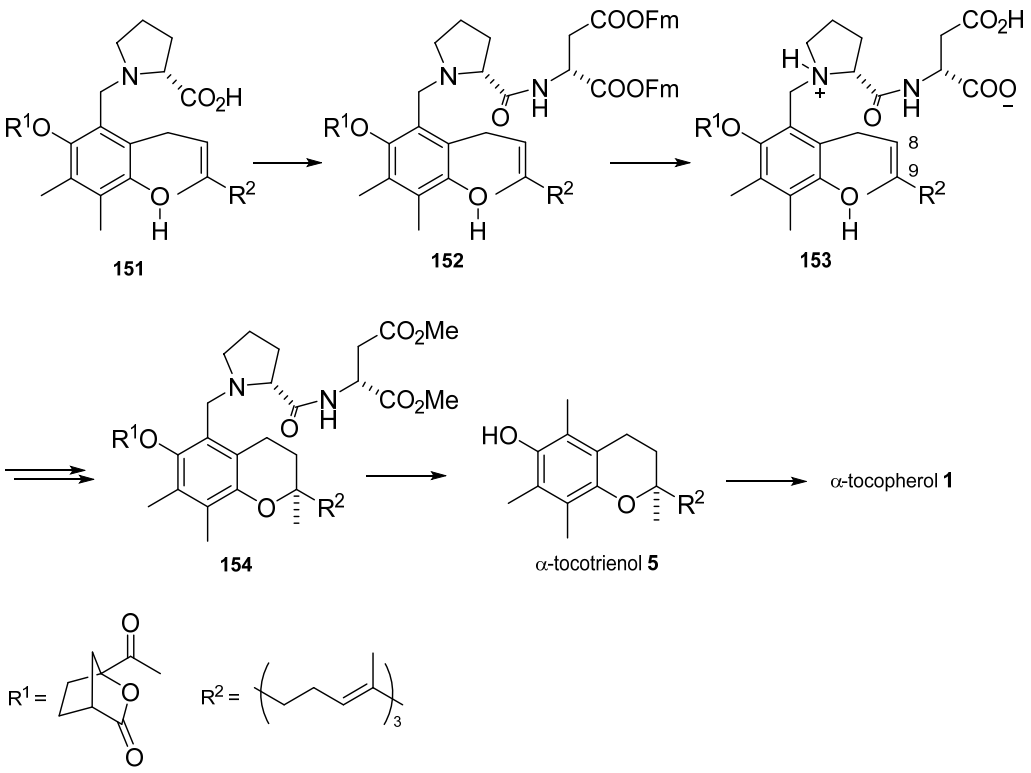
Scheme 33. Synthesis of α-tocopherol using a domino aldol/Michael addition.

Removal of the methyl ether protecting group using $BF_3.SMe_2/AlCl_3$ furnished (*R,R,R*)-α-tocopherol and (*S,R,R*)-α-tocopherol in yields of 29% and 26% respectively, over eight steps starting from phytol. Diastereomeric excess was measured at 93% and 94% respectively.

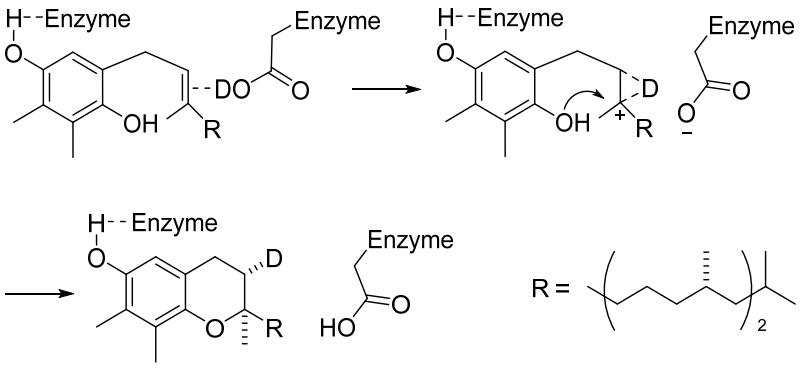


Scheme 34. Proposed mechanism for the aldol/oxa-Michael addition.

Woggon *et al*. also used chiral proline derivatives in a biomimetic synthesis inspired by a tocopherol cyclase enzyme (Schemes 35 and 36).[213, 214] The chiral auxiliary D-Pro-D-Asp was installed using a Mannich reaction with *N*-methylene-D-proline, followed by coupling with Fm-protected D-aspartate. Note that the use of a bulky R^1 substituent was required to force the peptide into a conformation that is close enough to the C-8 double bond. The key cyclisation of amide **153** follows an analogous mechanism to that of the cyclase enzyme (Scheme 36). In this way the chromane **154** was furnished, which after removal of the chiral auxillary and the camphanate ester gave α-tocotrienol in 65% *e.e*. Conditions developed by Pfaltz *et al*.[165, 215] enabled the catalytic hydrogenation of the side chain double bonds in an *R*/*S* ratio of > 99:1, eventually yielding α-tocopherol **1** in an overall yield of 1% over 16 steps.

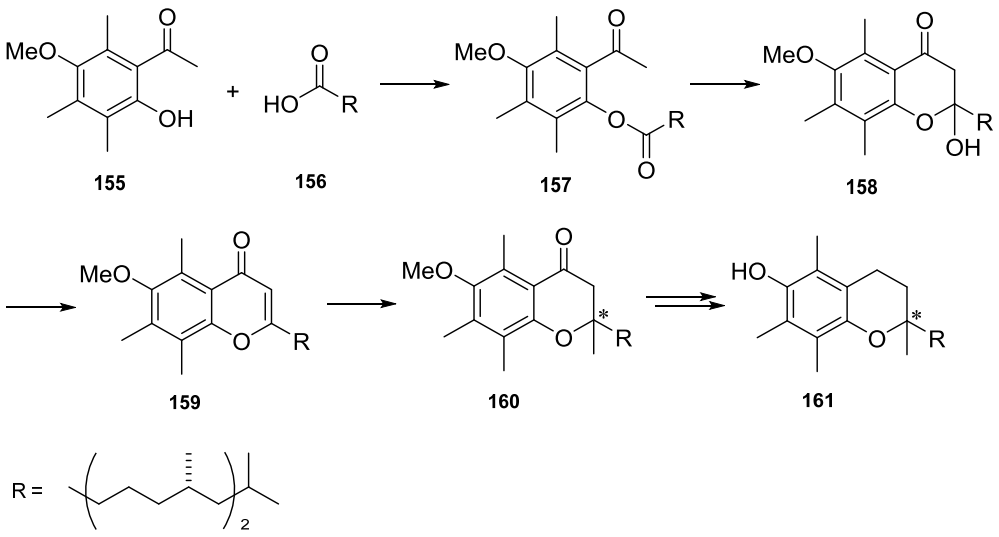


Scheme 35. Biomimetic synthesis of α-tocopherol **1**.



Scheme 36. Reaction mechanism of tocopherol cyclase.[213]

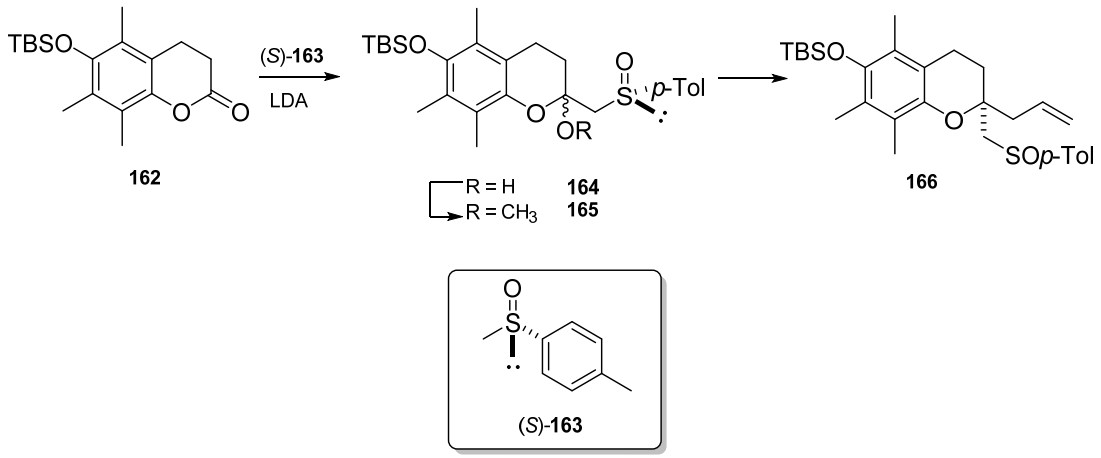
An alternative approach was explored by Termath *et al*. where the Ni-catalysed 1,4-addition of a methyl anion equivalent onto chromenone intermediate, **159**, was anticipated to yield an enantiomerically enriched chromane when chiral ligands were employed (Scheme 37).[216]



Scheme 37. Synthesis of α-tocopherol by 1,4-addition.

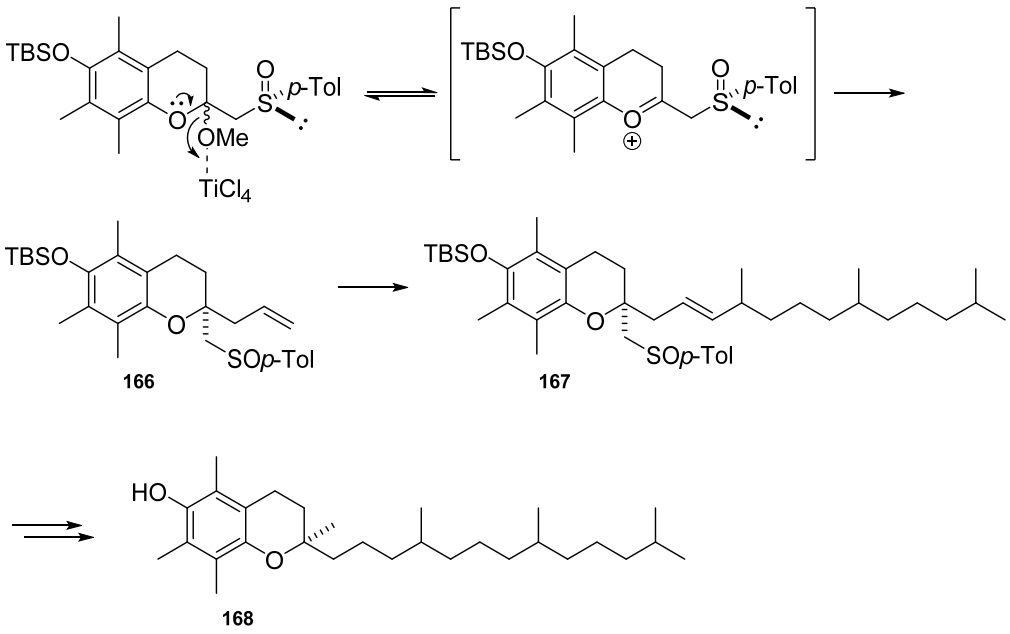
Acetophenone building block **155** was synthesised from trimethylhydroquinone in a yield of 85% over four steps, whilst carboxylic acid **156** was elaborated from (*R*,*R*)-hexahydrofarnesol in 96% yield. Treatment of ester **157** with KO*t*-Bu yielded the chromanone **158** in a Baker-Venkatamaran rearrangement,[217, 218] and subsequent dehydration with AcCl/MeOH gave the key chromenone **159**. Termath *et al*. had previously reported work on metal-catalysed, enantioselective 1,4-additions to cyclohexanone;[219, 220] however, treatment of chromenone **159** with $AlMe_3$ in the presence of a chiral Ni complex failed to provide any stereoselectivity. A maximum *d.e*. of 2% was observed across all the ligands screened. (2*RS*,4'*R*,8'*R*)-α-Tocopherol was obtained in an overall yield of 60% over 11 steps (longest linear sequence).

Colobert *et al*. synthesised (2*R*,4'*RS*,8'*RS*)-α-tocopherol using a sulfoxide-directed allylation as the key step (Scheme 38).



Scheme 38. Stereoselective synthesis of a chromane compound.

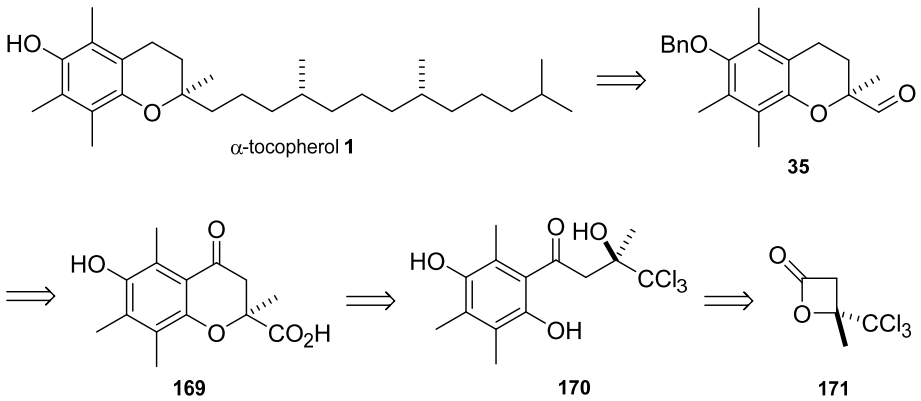
The treatment of the chroman-2-one **162** with the lithium anion of (*S*)-**163** gave chromanol **164**, which after reaction with trimethylorthoformate/*p*-toluenesulfonic acid (*p*-TsOH) gave the corresponding ketal. Treatment of ketal **165** with $TiCl_4$ and allyl trimethylsilane gave the sulfoxide **166** in 73% yield and > 99% *e.e*. The proposed mechanism is shown in scheme 39. Attack of upper face of the oxonium intermediate by allyl trimethylsilane rationalises the observed stereochemistry. A cross-metathesis reaction with **166** and 3,7,11-trimethyldodec-1-ene gave a compound with the full carbon skeleton of α-tocopherol, and a further three steps (desulfinylation, double bond hydrogenation and TBS deprotection) yielded (2*R*,4'*RS*,8'*RS*)-α-tocopherol **168** in ten steps and 24% overall yield.



Scheme 39. Sulfoxide-directed allylation.

1.10 Our Planned Synthesis of α-Tocopherol

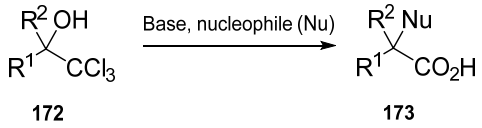
As a known precursor to α-tocopherol, aldehyde **35** should be accessible from the carboxylic acid **169**, which in turn should be the product of the intramolecular Jocic reaction of phenol **170** (Scheme 40). It was hoped that this phenol could ultimately be derived from the enantiomerically enriched β-lactone **171**. Given the importance of the key cyclisation step in setting the stereochemistry of chroman-4-one **169**, a detailed discussion of the Jocic reaction and the synthesis of trichlorocarbinols will follow.



Scheme 40. Preliminary retrosynthesis of α-tocopherol **1**.

1.11 The Jocic Reaction

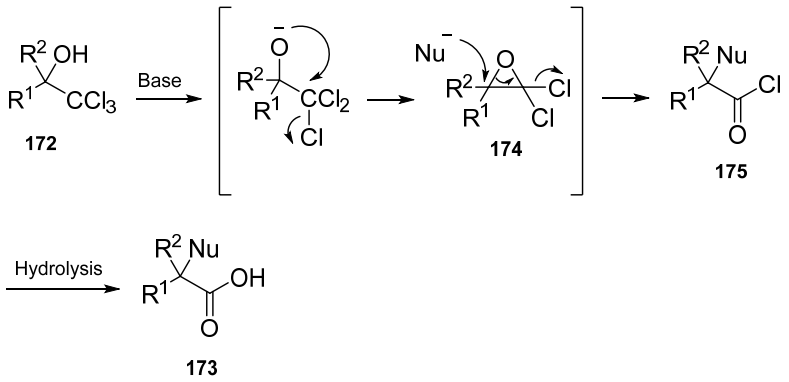
The transformation of trichlorocarbinols **172** into α-substituted carboxylic acids **173** under basic conditions is most commonly referred to in the literature as the Jocic reaction (Scheme 41).[221, 222]



172 **173**

Scheme 41. The Jocic reaction.

The accepted mechanism is shown in scheme 42. After deprotonation by base, the intramolecular displacement of chloride produces the *gem*-dichloroepoxide **174**. The regioselective, *stereospecific* S_N2 ring-opening of this epoxide by a nucleophile, followed by hydrolysis of the resulting acid chloride **175**, yields α-substituted carboxylic acids **173**.



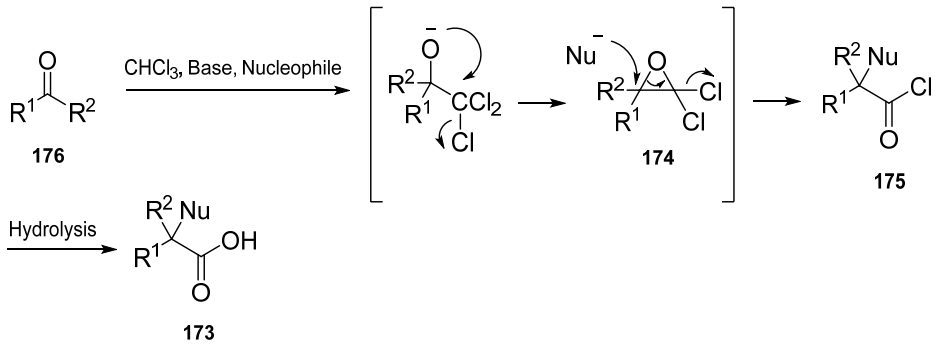
172 **174** **175** **173**

Scheme 42. General mechanism for the Jocic reaction.

The alkyl or aryl groups R^1 and R^2 can be widely varied and the reaction works with both organic and inorganic bases, in a variety of solvents. Many different nucleophiles have been employed and these will be discussed later.

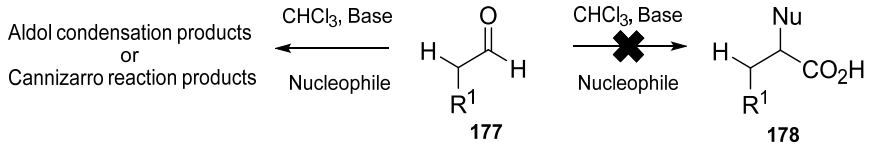
1.12 The Bargellini Reaction

The Bargellini reaction is a variation on the Jocic reaction where the trichlorocarbinol is not isolated but is generated *in situ* (Scheme 43).[223]



Scheme 43. General mechanism for the Bargellini reaction. R^1, R^2 = alkyl.

The mechanism goes through the same *gem*-dichloroepoxide **174** as the Jocic reaction, with the main differences being that the trichlorocarbinol is not isolated, and that neither R^1 nor R^2 are hydrogens. The reaction of aldehyde **177** with α-H fails to give carboxylic acid **178** under the same conditions due to competing aldol condensation reactions (Scheme 44). The reaction of aldehyde **177** with no α-H yields mainly the alcohol and carboxylic acid products of the Cannizzaro[224] reaction.



Scheme 44. Failure of aldehydes as substrates in the Bargellini reaction. R^1 = alkyl.

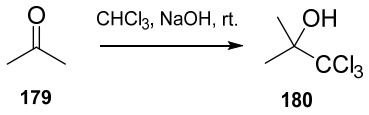
Similarly to the Jocic reaction, a variety of bases and nucleophiles have been explored and the reaction has found considerable use by researchers in the pharmaceutical industry. Examples of the Jocic and Bargellini reactions will be discussed later.

1.13 Synthesis of Racemic Trichlorocarbinols

The synthesis of racemic trichlorocarbinols can largely be separated into two groups; the addition of a trichloromethyl anion to a carbonyl compound, or the addition of nucleophiles to chloral (Cl_3CCHO) or related ketones. Examples of each are discussed in the following sections.

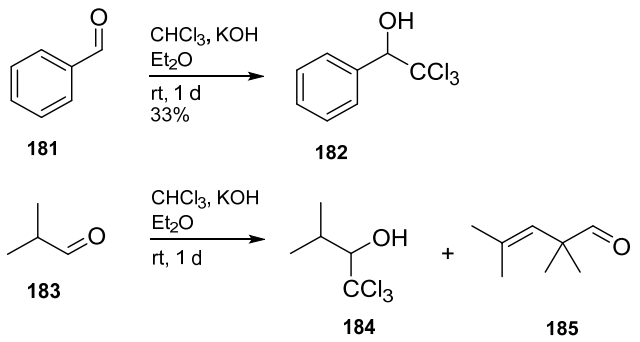
1.13.1 Trichloromethyl Anion Addition

One of the earliest examples of trichlorocarbinol synthesis *via* trichloromethide addition was from Willgerodt, who synthesised 1,1,1-trichloro-2-methylpropan-2-ol **180** in 1881 by the reaction of acetone with chloroform and sodium hydroxide (Scheme 45).[225, 226] Saljoughian *et al*. later reported that the optimal molar ratio of acetone:chloroform was 10:1, and that carrying out the reaction at -5 °C gave a yield of 71%.[227] The use KOH over NaOH gave higher yields.



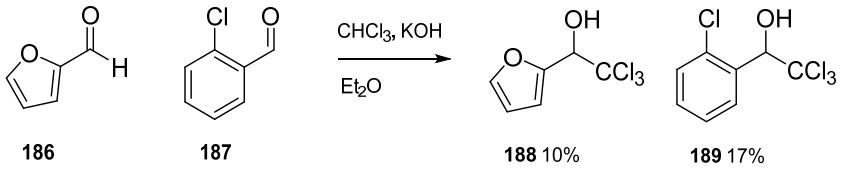
Scheme 45. Early synthesis of 1,1,1-trichloro-2-methylpropan-2-ol. Yield not reported.

Jocic was the first to use this reaction with aldehydes under the same conditions to give trichlorocarbinols (Scheme 46).[221] In addition to benzaldehyde **181** he also studied the reaction using isobutyraldehyde **183**. However, it was found that significant aldol condensation took place and he was unable to isolate the trichlorocarbinol **184** cleanly.

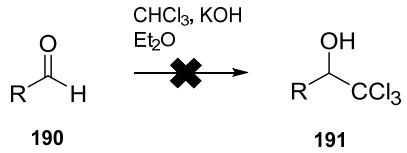


Scheme 46. Synthesis of 2,2,2-trichloro-1-phenylethan-1-ol by Jocic.

This chloroform/hydroxide methodology was later extended to furfural **186** and *o*-chlorobenzaldehyde **187** by Howard (Scheme 47).[228, 229] He also tested the reaction using aliphatic aldehydes (**190**, Scheme 48), but found that aldol condensation was prevalent as Jocic had reported previously. Howard also reported that bromoform could be used in place of chloroform to yield the tribromo compound.[230]

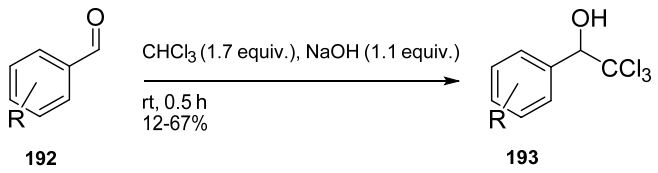


Scheme 47. Synthesis of 2,2,2-trichloro-1-(furan-2-yl)ethan-1-ol.



Scheme 48. Attempted synthesis of aliphatic trichlorocarbinols. R = CH_3CH_2, $CH_3CH_2CH_2$, $(CH_3)_2CHCH_2$.

Both Howard and Jocic used less than equimolar quantities of hydroxide in their experiments since they assumed that it served as a catalyst for the reaction, which accounts partly for the low yields they obtained. Bergmann *et al.* used a series of substituted benzaldehydes with equimolar potassium hydroxide in order to obtain improved yields of the addition product (Scheme 49).[231]



192 193

Scheme 49. Improved synthesis of aryl trichlorocarbinols. R = *o*-CH_3, *m*-CH_3, *p*-CH_3, *o*-OCH_3, *m*-OCH_3, *p*-OCH_3, *o*-Cl, *m*-Cl, *p*-Cl.

Viehe and Valange used sodium amide as the base for the addition of trichloromethide to several carbonyl compounds (Table 7).[232]

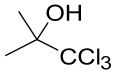
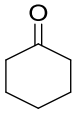
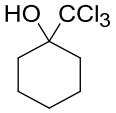
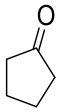
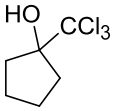
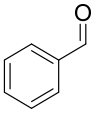
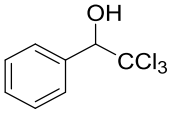
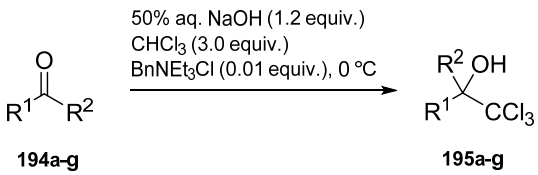
carbonyl	product	yield (%)	carbonyl	product	yield (%)
		86[a]			74[c]
		93[b]			32[d]

Table 7. Synthesis of trichlorocarbinols using sodium amide base. Reagents and conditions: [a] $CHCl_3$ (1.0 equiv.), $NaNH_2$ (1.0 equiv.); [b] $CHCl_3$ (4.0 equiv.), $NaNH_2$ (1.2 equiv.); [c] $CHCl_3$ (3.0 equiv.), $NaNH_2$ (1.0 equiv.); [d] $CHCl_3$ (1.0 equiv.), $NaNH_2$ (1.0 equiv.). All reactions were carried out in liquid ammonia solvent at -80 °C.

These reaction conditions gave good yields for the ketones studied. When benzaldehyde was used a lower yield was obtained due to the competing addition of amide and the Cannizzaro side reaction.

Merz and Tomahogh used a phase transfer-catalysed reaction to synthesise trichlorocarbinols from both aldehydes and ketones (Table 8).[233]

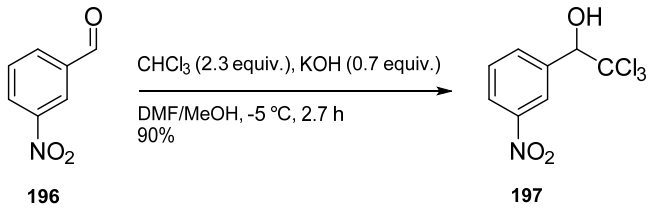


entry	R^1	R^2	time (min)	195 yield (%)
a	Phenyl	H	90	80
b	*p*-$CH_3OC_6H_4$	H	120	62
c	*i*-Propyl	H	30	34
d	Methyl	CH_3	15	69
e	Ethyl	CH_3	15	13
f	Cyclopentanone		15	33
g	Cyclohexanone		20	23

Table 8. Synthesis of trichlorocarbinols using a phase transfer catalyst.

Cannizzaro and aldol reactions are the major side reactions when strongly basic conditions are used in the presence of aldehydes.[224, 234] The use of biphasic conditions reduces the contact that the organic compounds have with the basic aqueous layer and this suppresses these side reactions. Even under these conditions the yield of aliphatic compound **195c** was still low. Merz and Tomahogh put the unreactivity of **194e** down to steric hindrance since the yields with cyclic analogues were higher. Additionally, it was found that a low temperature was necessary to obtain reasonable yields since at higher temperatures the Cannizzaro reaction predominated over addition of trichloromethide.

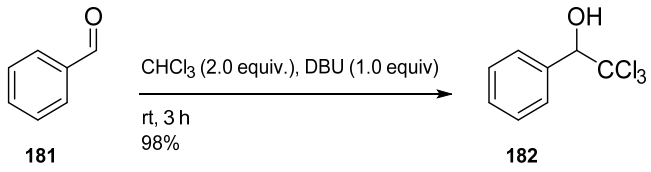
Wyvratt *et al*. developed a high yielding method for the synthesis of both secondary and tertiary trichlorocarbinols, with no evidence of competing Cannizzaro reactions (Scheme 50).[235]



Scheme 50. Wyvratt synthesis of 2,2,2-trichloro-1-(3-nitrophenyl)ethan-1-ol **197**.

The base was used in a methanolic solution in order to obtain a homogenous mixture, since lower yields were obtained with solid base in DMF alone. In addition to 3-nitrobenzaldehyde **197**, benzaldehyde (99%), *p*-anisaldehyde (97%), isobutyraldehyde (70%) and cyclohexanone (68%) were also used as substrates in the reaction. The lower yields obtained for the enolisable carbonyl compounds is due to the competing aldol condensation. Wyvratt attributed the success of the procedure to the enhanced nucleophicity of the trichloromethyl anion in DMF solvent.

Aggarwal and Mereu developed an amidine-promoted protocol for the addition of chloroform to benzaldehyde (Scheme 51).[236]



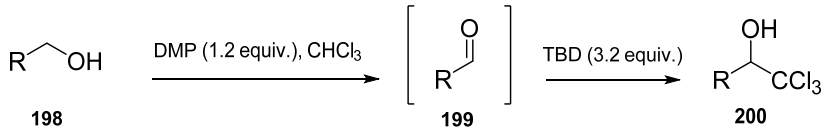
Scheme 51. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted addition of chloroform to benzaldehyde.

Both amidines and guanidines were found to promote the reaction; the use of these non-nucleophilic organic bases completely suppressed any Cannizzaro side reactions. Table 9 shows a selection of results obtained by Aggarwal. Noteworthy is the observation that enolisable aldehydes and ketones (entries **e-g**) gave better yields than had previously been reported. This is due to competing side reactions being suppressed by the mild conditions. The yield for mesitaldehyde (entry **d**) is lower due to steric hindrance.

entry	carbonyl compound	time (h)	trichlorocarbinol yield (%)
a	Benzaldehyde	3	98
b	*o*-Chlorobenzaldehyde	4	94
c	*p*-Anisaldehyde	6	95
d	Mesitaldehyde	1	25
e	Propanal	2	80
f	Acetone	24	75
g	Cyclohexanone	24	84

Table 9. Selection of results from Aggarwal *et al*. Reactions were performed in absence of solvent at room temperature using a carbonyl compound:$CHCl_3$:DBU ratio of 1:2:1.

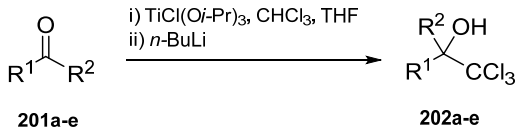
Snowden *et al*. developed a one-pot synthesis of trichlorocarbinols from primary alcohols (Table 10).[237] By sequential addition of Dess-Martin periodinane (DMP) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to the alcohol in $CHCl_3$, trichlorocarbinols **200** were synthesised in reasonable to good yield. 1,1,3,3-Tetramethylguanidine (TMG) and DBU gave inferior results when used as the base. By removing the need to isolate the aldehyde **199** the authors were able to trichloromethylate more sensitive compounds, such as 2-thienylmethanol **198f**, which formed a sensitive aldehyde that proved difficult to isolate and trichloromethylate by other methods. Propargylic alcohol **198g** was an unsuitable substrate since several byproducts were formed upon addition of base to the intermediate ynal.



entry	R	time (h)	200 yield (%)
a	*p*-OCH_3Ph	24	83
b	Ph	8	87
c	*p*-NO_2Ph	6	85
d	$PhCH_2CH_2$	30	71
e	$CH_3(CH_2)_8$	30	60
f	Thiophen-2-yl	48	61
g	PhCCH	10	34

Table 10. One-pot oxidation/trichloromethylation of primary alcohols. Reactions were conducted on a 1 mmol scale.

Li *et al*. used an organotitanium reagent to prepare trichlorocarbinols from enolisable ketones (Table 11).[238] Enolisation and steric hindrance remain problems in the preparation of trichlorocarbinols from carbonyl compounds with α-protons. In searching for a solution to this issue, Li *et al*. noted that organotitanium reagents had been shown to be superior to traditional Grignard reagents for additions to sterically hindered and/or enolisable ketones.[239, 240] Thus, when $TiCl(O\textit{i}\text{-}Pr)_3$ was used as an additive in the base-promoted addition of chloroform, a range of ketones were found to be suitable substrates. Notably, the highly enolisable ketone **201c** gave trichlorocarbinol **202c** in moderate yield.



201a-e 202a-e

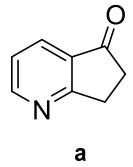
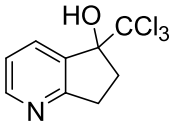
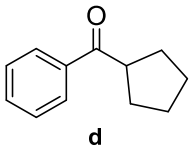
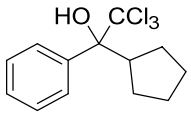
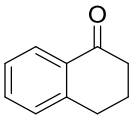
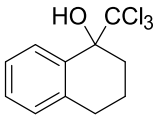
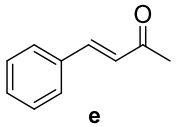
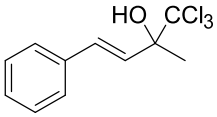
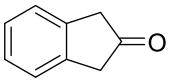
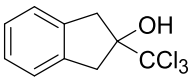
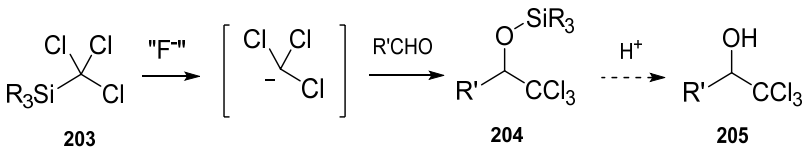
carbonyl	product	yield (%)	carbonyl	product	yield (%)
 **a**		95	 **d**		84
 **b**		93	 **e**		96
 **c**		45			

Table 11. Reagents and conditions: $CHCl_3$ (5.0 equiv.), *n*-BuLi (5.0 equiv.), $TiCl(O\textit{i}\text{-}Pr)_3$ (2.0 equiv.), THF, -60 °C, 4 h.

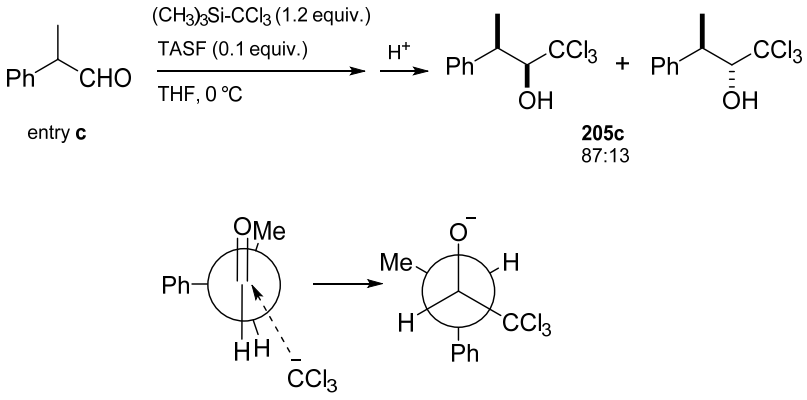
Organometallic reagents of the type LiH_2X, $LiHX_2$ and LiX_3 are known to add to electrophiles; however they are highly thermolabile and their reactions require low temperatures.[241-245] α-Halo organosilanes were investigated by Hiyama and Fujita as an alternative method for generating halo-carbanions for use in organic synthesis (Table 12).[246] Treatment of the organosilane **203** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) generated the corresponding carbanion, which readily added to aldehydes. When 2-phenylpropanal was used as the aldehyde (Table 12, entry **c**) the major product was the (2*S*,3*R*)-diastereomer. The use of more bulky organosilanes (e.g R = $PhMe_2$ or *t*-$BuMe_2$) did not significantly alter this ratio, indicating that the selectivity arises from the "naked" trichlorocarbanion.



203 204 205

entry	R	R’	205 yield (%)[a]
a	CH_3	Ph	77[b]
b	CH_3	*n*-$C_{10}H_{21}$	79[c]
c	CH_3	PhCH(CH_3)	75[d]

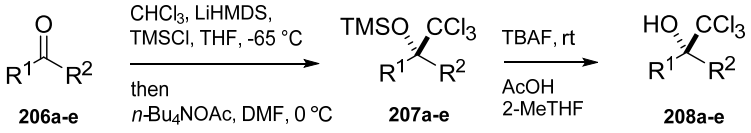
Table 12. [a] Isolated after desilylation (1M HCl/MeOH, rt, 0.25-0.5 h). Reagents and conditions: [b] TASF (0.1 equiv.), THF, rt, 8 h; [c] TASF (0.1 equiv.), THF, 0 °C, 12 h; [d] TASF (0.25 equiv.), THF, 0 °C, 4 h. In all entries 1.2 equiv. of silane was used. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.



Scheme 52. Explanation for the observed selectivity using a Felkin-Anh model.

Although the TMS-CCl_3 reagent had been shown above to add to aldehydes in useful yields, and later extended to ketones by Fujita *et al.*,[247] syntheses of the reagent itself were generally low yielding;[248-250] although more recently yields of 65-70% have been reported.[251] The reaction of TMS-CCl_3 with electrophiles has also been catalysed by sodium formate[252] and by flash pyrolysis.[253] Trimethylsilyl trichloroacetate has also been used as a transfer agent.[254, 255]

During scale-up studies Henegar and Lira developed a protocol for *in situ* generation of TMS-CCl_3 and addition to carbonyl compounds, thus avoiding the need to isolate and handle the reagent (Table 13).[256]



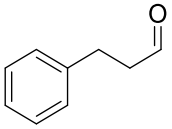
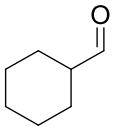
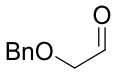
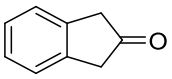
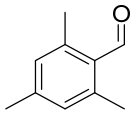
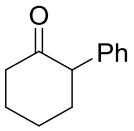
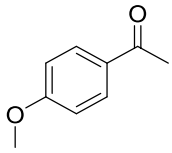
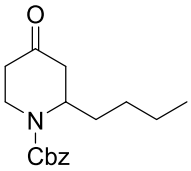
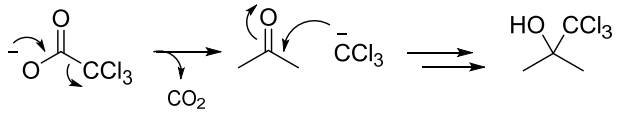
entry	carbonyl compound	207 yield (%)	entry	carbonyl compound	207 yield (%)
a		85	**f**		96
b		96	**g**		36
c		42	**h**		98
d		96[a]	**i**		95
e		-[b]			

Table 13. [a] Isolated as a > 20:1 mixture of diastereoisomers. [b] Not isolated, the deprotected carbinol was obtained in a yield of 65% over two steps and as a > 20:1 mixture of diastereoisomers.

The reaction was successful with a range of carbonyl compounds. Notably, high diastereoselectivity was obtained for entries **d** and **e**, where for **207d** the addition of

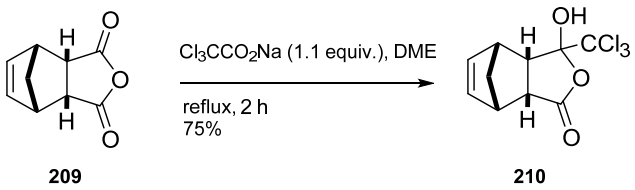
TMS-CCl_3 was established to occur *trans* to the substituent on the ring. Compounds which readily enolised (entries **c** and **g**) gave lower yields.

Whilst studying the thermal decarboxylation of trichloroacetate salts to generate dichlorocarbenes, Wagner *et al*. found that when acetone or butanone were used as the solvent addition of CCl_3 anion occurred, according to Scheme 53.[257, 258]



Scheme 53. Addition of trichloromethyl anion to acetone *via* decarboxylation of trichloroacetate salts.

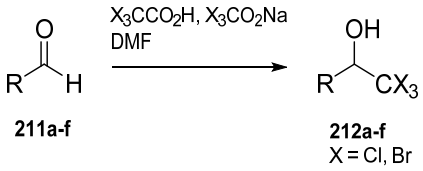
Winston *et al*. noted this observation and used the same conditions to prepare the trichlorocarbinol **210** in reasonable yield (Scheme 54).[259, 260] This appears to be the first reported attempt to use the thermal decarboxylation of trichloroacetate as a deliberate method for introducing the trichloromethyl group into organic structures.



209 **210**

Scheme 54. Synthesis of trichloromethylhydroxy lactone **210**.

Corey and Link further developed a general synthesis of trichlorocarbinols from aldehydes (Table 14).[261] By avoiding the use of a strong base, neither Cannizzaro nor aldol reaction side products were observed, as shown by the high yields obtained from aldehydes containing α-protons (entries **a**, **c**, **e** and **f**). Mild conditions and simplicity have allowed this procedure to find wide use for the synthesis of trichlorocarbinols, as will be seen later in the chapter.



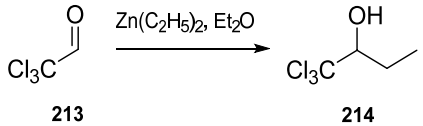
211a-f 212a-f
X = Cl, Br

entry	aldehyde	TCA/NaTCA (equiv.)	time (h)	212 yield (%)
a	Hydrocinnamaldehyde	1.5	0.5	97
b	Cinnamaldehyde	1.5	0.75	95
c	Cyclohexanecarboxaldehyde	1.5	1	84
d	Pivaldehyde	9.0	9	76
e	Diphenylacetaldehyde	13.5	36	59
f	3,4,5-trimethoxyphenylacetaldehyde	10.0	12	74

Table 14. Reactions were run at 23 °C (entries **a**-**d**) or 4 °C (entries **e** and **f**). TCA = trichloroacetic acid; NaTCA = sodium trichloroacetate.

1.13.2 Nucleophilic Addition to Chloral

The addition of nucleophiles to chloral to yield trichlorocarbinols considerably predates trichloromethide addition to carbonyl compounds; as early as 1858 ammonia had been used to yield the amino alcohol by Staedeler.[262] The first example of a carbon-based nucleophile being used in this way is from Garzarolli, who reported the reaction of diethyl zinc with chloral to yield 1,1,1-trichlorobutan-2-ol **214** (Scheme 55).[263]

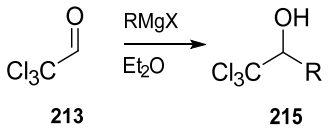


213 214

Scheme 55. Reaction of chloral with diethyl zinc.

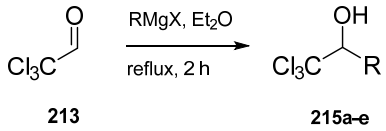
Jocic first used the reaction of phenylmagnesium bromide with chloral to give 2,2,2-trichloro-1-phenylethan-1-ol **215** (Scheme 56).[222] A yield of 61% was obtained by

Riemschneider for the same reaction.[264] Kharasch *et al*. obtained a yield of 60% for the reaction of methylmagnesium bromide with chloral.[265]



Scheme 56. Grignard reagent addition to chloral. R = Ph, Me.

A range of different Grignard reagents were studied by Howard (Table 15).[266, 267]



entry	**R**	**yield** (%)
214	Ethyl	32
a	Propyl	24
b	Butyl	41
c	*i*-Propyl	41
d	Benzyl	19

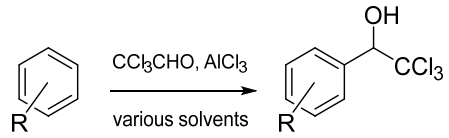
Table 15. Reaction of chloral with Grignard reagents.

Yields for the reaction of chloral with Grignard reagents that contain β-hydrogens are typically lower due to oxidation of the reagent, yielding significant quantities of reduced chloral (trichloroethanol).[268] An expanded range of Grignard reagents have since been explored by other authors and were found to give reasonable yields.[269-271]

When aryl trichlorocarbinols are required, Friedel-Crafts procedures are useful. The earliest reports, dating back to 1887, detail the reaction of benzene and chloral in the presence of $AlCl_3$, to yield 2,2,2-trichloro-1-phenylethan-1-ol.[272, 273] Dinesmann demonstrated the generality of the reaction by using toluene, *p*-xylene and anisole as

the aromatic starting materials.[274] $AlCl_3$ is generally used as the Lewis acid catalyst but BF_3 has also been shown to be effective.[275] When sulfuric acid is used as the catalyst the products are exclusively diaryltrichloroethanes.[276]

Reeve *et al*. studied a variety of aromatic compounds in the Friedel-Crafts reaction with chloral (Table 16).[277]



216a-j **217a-j**

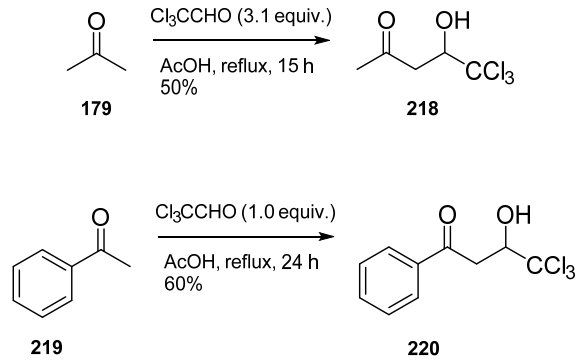
entry	216	ratio 216:chloral	$AlCl_3$ (equiv.)	solvent	217 yield (%)
a	Benzene	Excess[a]	0.22	Benzene	80
b	Napthalene	0.5	0.15	Nitrobenzene	61
c	Anisole	Excess[a]	0.20	Anisole	39
d	2,4-Dichloroanisole	1.0	2.0	CS_2	0
e	2,4-Dichlorophenol	0.9	2.1	CS_2	60
f	2,5-Dichlorobenzene	Excess[a]	0.9	2,5-Dichlorobenzene	76
g	Fluorobenzene	1.0	1.0	CS_2	62
h	Chlorobenzene	Excess[a]	0.2	Chlorobenzene	50
i	Bromobenzene	Excess[a]	0.2	Bromobenzene	55
j	Iodobenzene	1.0	1.0	CS_2	30

Table 16. Friedel-Crafts reaction of aromatic compounds with chloral. [a] Excess indicates that 7-10 equivalents were employed.

In general, the aromatic compound was used as both reactant and solvent. When CS_2 was used as the solvent a complex of aryltrichlorocarbinol/$AlCl_3$ precipitated out of solution, so a stoichiometric quantity of $AlCl_3$ was required for these reactions. The molar equivalents of $AlCl_3$ required varies with the reactivity of the aromatic substrate.

Rezende *et al*. established that the optimum equivalent of $AlCl_3$ was 0.2 for substrates less reactive than benzene and 0.4 for substrates more reactive than benzene.[278]

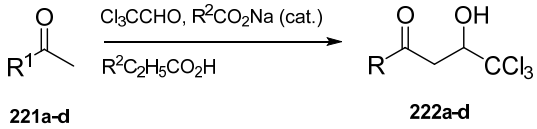
Much like the Friedel-Crafts acylation reaction has found use in the synthesis of aryl trichlorocarbinols, the aldol reaction can be used to synthesise alkyl trichlorocarbinols. An early example of this from Koenigs in 1892 is shown in scheme 57.[279]



Scheme 57. Aldol condensation of acetone and acetophenone with chloral.

Note that the reaction stops after the addition of one chloral molecule. Similar results were reported when the reactions were carried out in the absence of solvent.[280]

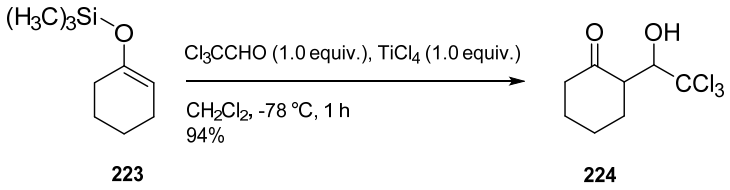
Reeve studied the condensation of a further four methyl ketones with chloral (Table 17).[281] This study was undertaken partly to resolve discrepancies in the literature as to the regiochemistry of the aldol adduct from **221b**. Breusche and Keskin[282, 283] stated that condensation occurred at the methyl group, while Caujolle *et al*. believed that condensation occurred at the methylene group.[284] Reeve *et al*. confirmed that addition occurred at the methyl group of **221b**, indicating that the enol formation was kinetically controlled. Steric hindrance is also a factor since butanone undergoes reaction at both methylene and methyl sites.[285]



entry	R^1	R^2CO_2Na (equiv.)	temperature (°C)	time (h)	222 yield (%)
a	CH_3	0.25	94	88	50
b	$(CH_3)_2CHCH_2$	0.25	100	108	59
c	$(CH_3)_2CCH$	0.25	73	91	41
d	PhCHCH	0.30	80	24	22

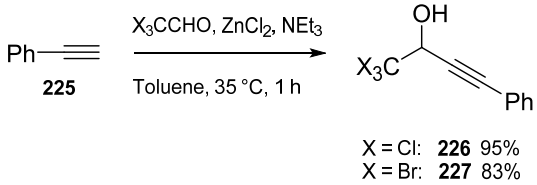
Table 17. Ketones were used in slight excess (1.25 equiv.) with respect to chloral. $R^2 = C_2H_5$ (entries **b** and **c**); $R^2 = CH_3$ (entries **a** and **d**).

Banno *et al*. used $TiCl_4$ to mediate the aldol reaction between silyl enol ether **223** and chloral (Scheme 58).[286, 287] The reaction was rapid and high yielding even at -78 °C, and no byproducts from poly- or self-condensation were detected.



Scheme 58. Crossed-aldol reaction using a silyl enol ether

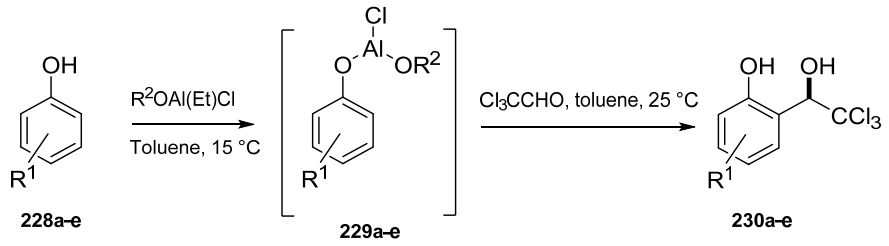
Jiang *et al*. used $ZnCl_2/NEt_3$ to promote the alkynation of both chloral and bromal (Scheme 59).[288]



Scheme 59. Reagents and conditions: alkyne **225** (1.1 equiv.), Cl_3CCHO (1.0 equiv.), $ZnCl_2$ (1.5 equiv.), NEt_3 (1.5 equiv.).

1.14 Synthesis of Enantiomerically Enriched Trichlorocarbinols

Considerable effort has gone into the asymmetric syntheses of trichlorocarbinols due to the stereospecific nature of their reaction with nucleophiles under basic conditions (see earlier, Scheme 41). An early example from Casiraghi *et al*. is shown in table 18.[289, 290]



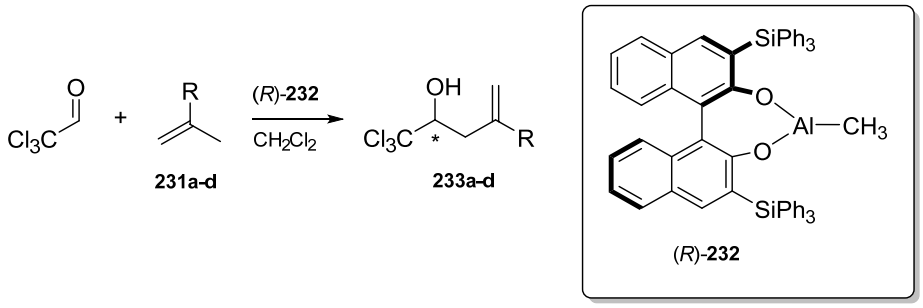
entry	phenol	230 yield (%)	*e.e.* (%)	configuration
a	Phenol	96	34	*R*
b	*p*-Methylphenol	97	48	*R*
c	*o*-Methylphenol	65	76	*R*
d	*o*-Isopropylphenol	78	54	*R*
e	2,5-Dimethylphenol	55	80	-[a]

Table 18. R^2 = (-)-menthyl. Alkoxide **229** was prepared *in situ* from phenol (1.0 equiv.), (-)-menthol (1.0 equiv.) and Et_2AlCl (1.0 equiv.). [a] Not determined.

The authors used a chiral alkoxyaluminium chloride promoter in the *o*-alkylation of phenols **228a-e**. Presumably coordination of chloral to the phenoxy-aluminium complex **229** in the reaction transition state provides the asymmetric induction, although the *e.e.* values obtained were variable. Stoichiometric quantities of aluminium reagent were also required.

Yamamoto *et al*. disclosed the first asymmetric ene-reaction catalysed by the chiral Lewis acid (*R*)-**232** (Table 19).[291] The enantiomeric excesses obtained were fairly low, and stoichiometric quantities of Lewis acid catalyst were required to maximise the *e.e.*

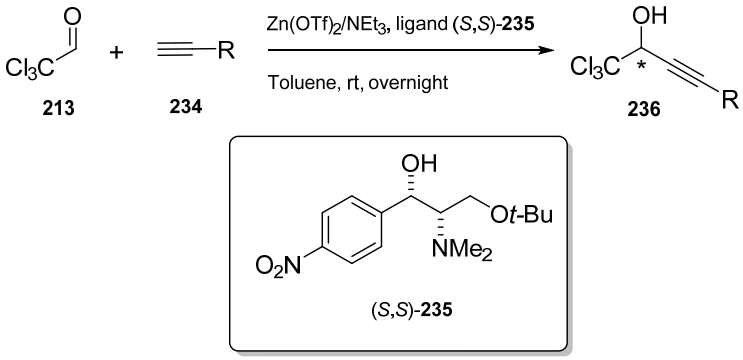
values. A chiral poisoning strategy has also been used to yield a catalyst for the asymmetric ene reaction with chloral, albeit with lower *e.e.* than those in the examples above.[292]



entry	R	233 yield (%)	*e.e.* (%)
a	CH_3	79[a]	78
b	$(CH_2)_5CH_3$	99[b]	64
c	Ph	40[c]	76
d	SPh	69[c]	57

Table 19. Reagents and conditions: [a] (*R*)-**232** (0.2 equiv.), 4 Å molecular sieves, CH_2Cl_2, -78 °C, 1.5 h; [b] (*R*)-**232** (1.1 equiv.), CH_2Cl_2, -20 °C, 1 h; [c] (*R*)-**232** (1.1 equiv.), -78 °C, 1-2 h. All reactions were carried out with the alkene in slight excess (1.2 equiv.).

Jiang *et al*. reported the catalytic, asymmetric alkynation of chloral to yield propargylic alcohols **236** (Table 20).[293] Carreira and co-workers had previously reported the first *catalytic*, asymmetric addition of terminal acetylenes to aldehydes using $Zn(OTf)_2$, (+)- or (-)-*N*-methylephedrine and NEt_3.[294-297] Jiang *et al*. expanded on this work and studied the reaction of a variety of acetylenes **234** with chloral. Ligand (*S*,*S*)-**235** was found to provide greater selectivity than *N*-methylephedrine used by Carreira. In addition, the ligand could be recovered unchanged in 96% yield and recycled without loss of enantioselectivity.

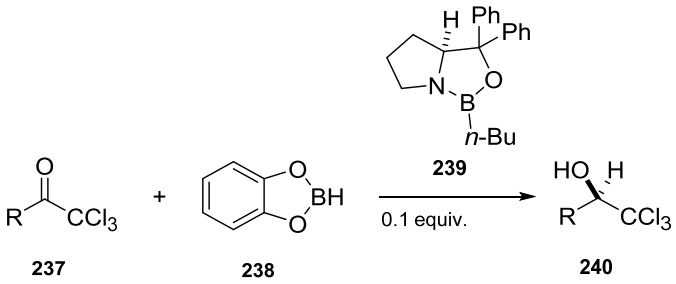


entry	R	236 yield (%)	*e.e.* (%)
a	Ph	96	94
b	2-Phenylethyl	76	98
c	Cyclopropyl	90	96
d	*t*-Butyl	60	93
e	*n*-Butyl	79	98
f	Trimethylsilyl	70	92
g	$CH_2OTBDMS$	71	98
h	Cyclopentylmethyl	95	95

Table 20. Reagents and conditions: alkyne (1.1 equiv.), $Zn(OTf)_2$ (0.50 equiv.), NEt_3 (0.75 equiv.), (*S*,*S*)-**235** (0.55 equiv.). All reactions were carried out in toluene at room temperature.

1.14.1 Asymmetric Reduction

Corey and co-workers reported the highly enantioselective borane reduction of ketones, catalysed by chiral oxazaborolidines.[298-301] They applied this method to trichloroketones **237** (Table 21),[302] which were readily synthesised in two steps from the corresponding aldehydes.[261, 303] Excellent enantioselectivities were achieved for all the ketone substrates screened, although low temperatures were necessary to maximise the *e.e.* values (entries **f** and **g**).



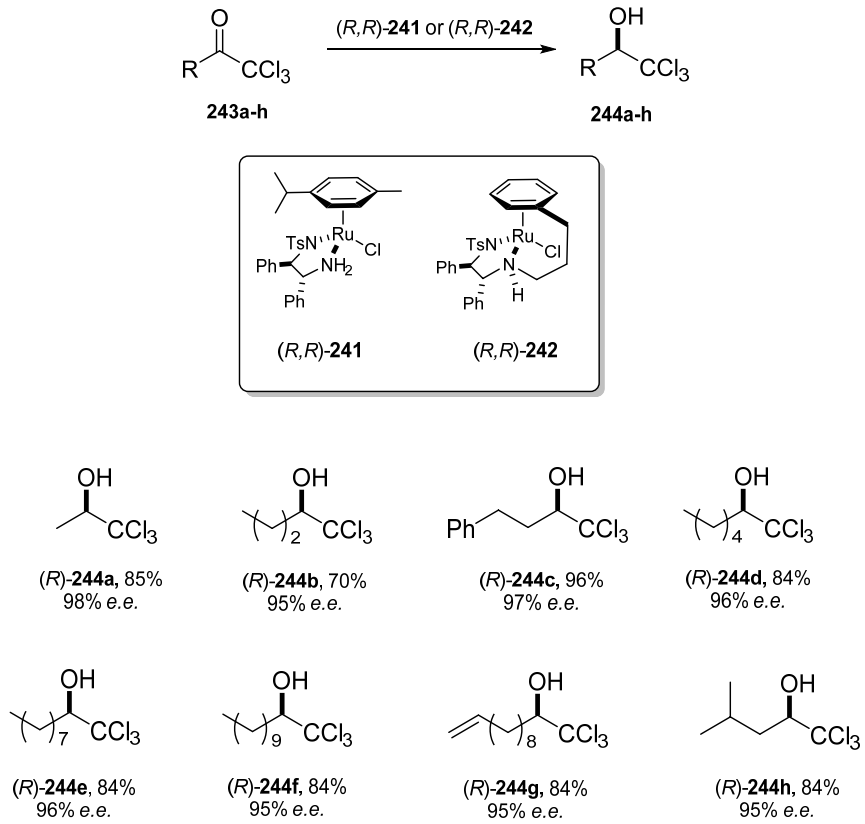
entry	R	solvent	temp, °C (time, h)	*e.e.* (%)
a	*n*-C_5H_{11}	Toluene	-60 (12)	95
b	$C_6H_5(CH_2)_2$	Toluene	-78 (12)	95
c	*p*-$C_6H_5C_6H_4CH_2$	CH_2Cl_2	-44 (10)	96
d	2-Naphthylmethyl	CH_2Cl_2	-23 (1.7)	93
e	Cyclohexyl	CH_2Cl_2	-28 (48)	92
f	*t*-Butyl	Toluene	-20 (56)	98
g	*t*-Butyl	Toluene	+23 (12)	95

Table 21. All reactions were initiated at -78 °C and brought to the indicated temperature after one hour.

Enantioselective reductions of this type have also been carried out using stoichiometric pinene-derived boranes in place of the oxazaborolidine **239**, although the reactions with trichloroketones were extremely slow (22 days to reach completion).[304, 305]

Noyori first introduced the ruthenium catalyst (*R,R*)-**241** for the asymmetric transfer hydrogenation of acetophenones[162, 306, 307] and Wills later improved the catalytic activity of the reaction by developing the tethered analogue (*R,R*)-**242**.[308, 309] Perryman *et al*. reported the reduction of trichloroketones **243** using both of these catalysts (Scheme 58).[310] High enantioselectivities were obtained for a variety of alkyl trichloroketones, however when R = aryl the selectivity was reduced due to competition between Ar and CCl_3 for coordination to the arene ligand. This is

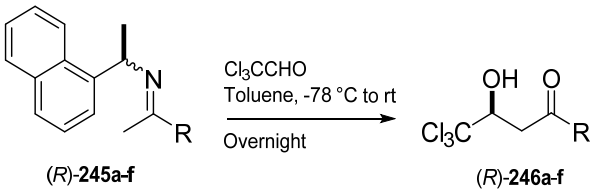
exemplified by the fact that the 2,2,2-trichloroacetophenone was reduced with the opposite sense of asymmetric induction compared to acetophenone itself, albeit with lower *e.e.* The difference in *e.e.* values obtained from using tethered catalyst (*R*,*R*)-**242** was typically small.



Scheme 60. Yields and enantiomeric excesses of trichloroketone reductions. Typical conditions: ketone (1.0 mmol), HCO_2H/NEt_3 (5:2, 0.5 mL), under N_2, 28 °C, 5-17 h. All results shown were obtained using catalyst (*R*,*R*)-**241**.

1.14.2 Organocatalysis

Although not catalytic, Funabiki *et al*. used chiral imines in a stereoselective aldol reaction with chloral to yield enantiomerically enriched β-trichloro-β-hydroxy ketones (Table 22).[311] Yields were moderate in comparison to other methods although the *e.e.* values were good. The reaction was also successful when chloral hydrate was used in place of chloral, with slightly worse enantioselectivity.

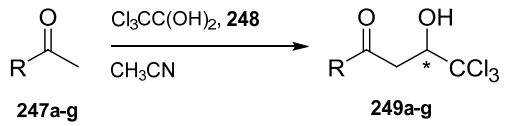


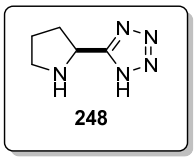
(*R*)-**245a-f** (*R*)-**246a-f**

entry	R	246 yield (%)	*e.e.* (%)
a	Ph	77	92
b	*p*-ClC_6H_4	76	90
c	*p*-$CH_3OC_6H_4$	51	85
d	2-Thienyl	45	81
e	Cyclohexyl	56	88
f	*t*-Butyl	40	81

Table 22. Reagents and conditions: chloral (1.0 equiv.), toluene, -78 °C to rt, overnight.

Yamamoto *et al*. reported an asymmetric, direct aldol reaction promoted by a proline-derived tetrazole catalyst (Table 23).[312] List and co-workers were the first to report proline as an effective asymmetric organic catalyst, which they used in several classes of reaction.[313-316] Yamamoto *et al*. used the proline-derived catalyst **248** to catalyse the aldol reaction of ketones **247a-g** with either chloral or chloral hydrate, and a high enantioselectivity was observed. This was the first example of an organocatalysed aldol reaction with a water-sensitive aldehyde component, and catalyst **248** was generally found to be more effective than proline alone.

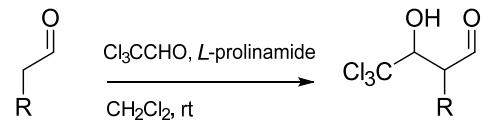




entry	R	temp, °C (time, h)	249 yield (%)	*e.e.* (%)[a]
a	$(CH_3)_2CH$	40 (24)	79[a]	97
b	$(CH_3)_2C{=}CH(CH_2)$	30 (24)	93[a]	82
c	$CH_3(CH_2)_3$	30 (36)	91[b]	82
d	CO_2Et	30 (24)	55	86
e	Ph	40 (48)	75	92 (*R*)
f	*p*-BrC_6H_4	40 (96)	76	91
g	2-Naphthyl	40 (96)	83	91

Table 23. Reagents and conditions: ketone (2.0 equiv.), **248** (5 mol%), CH_3CN. [a] The absolute configurations were not determined except for entry **e**. [b] Chloral was used in place of its monohydrate.

Gong *et al*. reported the first example of the cross-aldol reaction of chloral with aliphatic aldehydes (Table 24).[317] When *L*-proline was used as the catalyst, considerable self-condensation of aldehyde **250** was observed. The diastereo- and enantioselectivities were generally poor and a limited number of aliphatic aldehyde substrates were screened. In addition, a high catalyst loading of 30 mol% was required. The authors screened *L*-proline in their reaction conditions but not catalyst **248**, despite it having been shown to be highly effective.



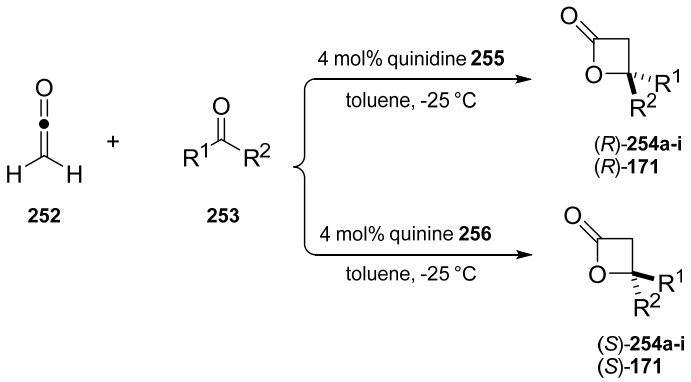
250a-d **251a-d**

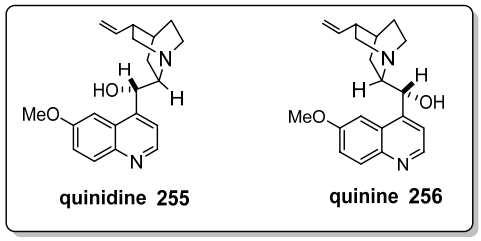
entry	R	251 yield (%)	*anti:syn*	*e.e.- anti* (%)	*e.e.- syn* (%)
a	Methyl	92	45:55	88	78
b	Ethyl	95	85:15	75	65
c	*i*-Propyl	35	80:20	70	65
d	*n*-Pentyl	81	69:31	69	31

Table 24. Reagents and conditions: Cl_3CCHO (1.0 equiv.), *L*-prolinamide (0.30 equiv.), CH_2Cl_2, rt, 24 h.

β-Lactones are masked aldol units, after ring opening by a suitable nucleophile. Wynberg *et al*. reported the first synthesis of enantiomerically enriched lactones **254**, *via* a cinchona alkaloid-catalysed aldol lactonisation (Table 25).[318-320] These lactones had previously only been synthesised in racemic form.[321, 322] The general catalytic cycle of the reaction is shown in scheme 61. Zwitterions such as **257** have been shown to have a relatively long lifetime,[323] providing the stereoselectivity when chiral tertiary amines (such as quinidine and quinine) are used.

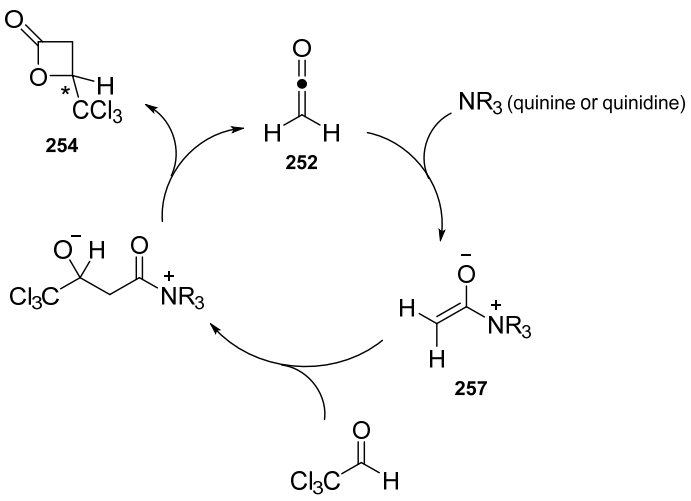
In general, much better enantioselectivities were obtained when using quinidine (**255**) as the catalyst. The reason for the difference in selectivity between quinine and quinidine is unclear, although it must be based on the relative position of the vinyl group in the transition states. Sufficient polarisation of the carbonyl is necessary for the reaction to take place. For example, no reaction was observed with monochlorinated aldehydes or with trichloroacetophenone (entry **g**). However, with *para*- electron withdrawing groups on the aromatic ring (entries **h** and **i)** the β-lactone was successfully isolated.





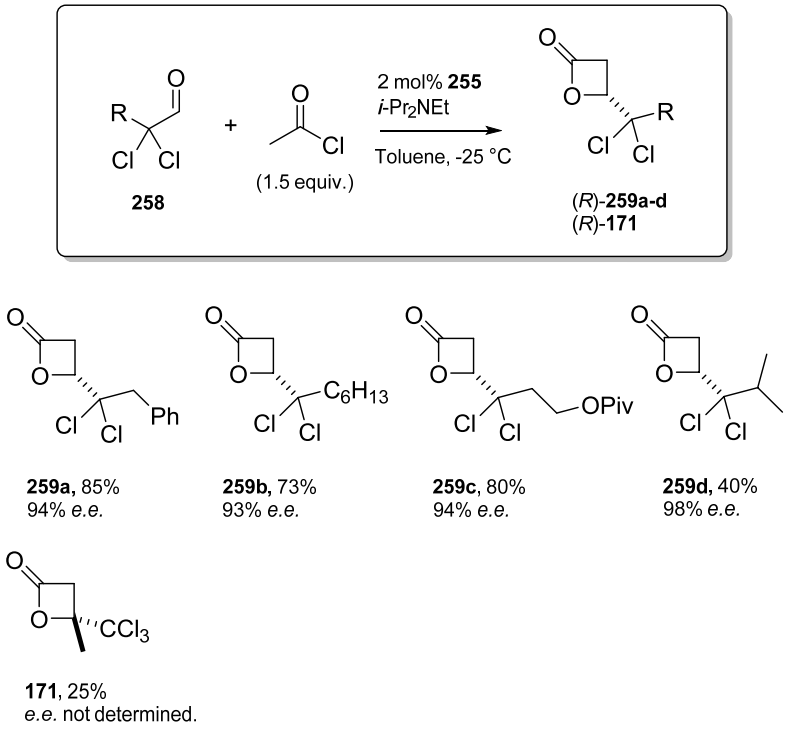
entry	R^1	R^2	*e.e.* (%) using catalyst		yield using quinidine catalyst (%)[b]
			quinidine	quinine	
a	CCl_3	H	98 [a]	76	89
b	CCl_2H	H	45	-	67
c	CCl_2CH_3	H	91	76	95
d	$CCl_2C_2H_5$	H	89	70	87
e	$CCl_2C_6H_5$	H	90	68	89
f	CCl_3	C_2H_5	-	-	Trace
g	CCl_3	C_6H_5	-	-	-
h	CCl_3	*p*-ClC_6H_4	90	65	68
i	CCl_3	*p*-$NO_2C_6H_4$	89	65	95
171	CCl_3	CH_3	94	85	72

Table 25. Catalytic, asymmetric synthesis of 2-oxetanones. [a] Identified as the (*R*)-enantiomer by conversion to malic acid. [b] The yield using quinine as the catalyst was not reported.



Scheme 61. Catalytic cycle for the tertiary amine-catalysed aldol lactonisation of ketene **252** with chloral.

Despite good *e.e.* values and high isolated yields, the need to use a ketene generator remained a limitation in Wynberg's protocol. Romo *et al*. used *in situ*-generated ketene to synthesise a number of chlorinated β-lactones (Scheme 62).[324]



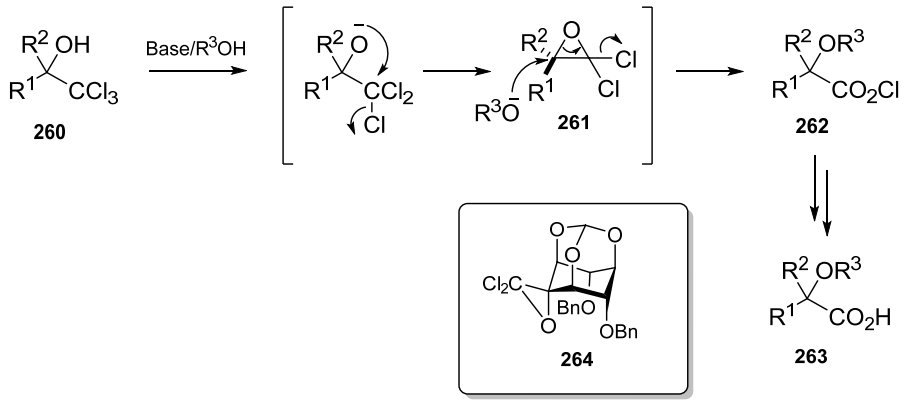
Scheme 62. The absolute configuration of **259b** and **171** were confirmed as (*R*) by comparison of optical rotations to literature data.[319, 320] The remaining lactones were assumed to be of the same configuration.

Treatment of acetyl chloride with Hunig's base (*i*-Pr_2NEt) generated the required ketene **252** by *in situ* dehydrochlorination, which then took part in the reaction with the aldehydes **258**. The tertiary amine used as a base has the potential to act as the nucleophilic catalyst, thus leading to racemisation; however the high *e.e.* values obtained, combined with the greater nucleophicity of the quinuclidine *N*-atom over Hunig's base,[323, 325] suggest that this does not take place.

1.15 Jocic Reactions with Racemic Trichlorocarbinols

1.15.1 Reactions with Oxygen-based Nucleophiles

Much of the early work on Jocic reactions involved the reaction of trichlorocarbinols **260,** with base in alcoholic solution to yield the α-alkoxy carboxylic acids **263** (Scheme 63). The reaction mechanism depicted is believed to be general regardless of the nature of the nucleophile, and support for the *gem*-dichloroepoxide intermediate comes both from the high stereospecificity of the reaction (discussed later) and from the isolation of pentachloro-propylene oxide **261** (where $R^1 = CCl_3$, $R^2 = H$).[326] More recently, the dichloroepoxide **264** was isolated and characterised by X-ray crystallography.[327]



Scheme 63. General Jocic reaction mechanism, depicted with an alkoxide nucleophile.

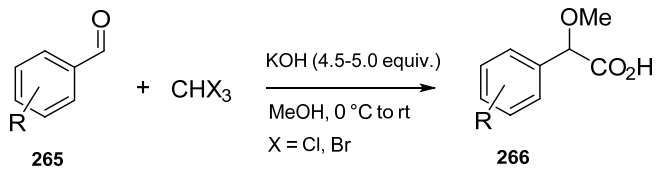
Table 26 lists some α-alkoxy carboxylic acids synthesised by Bergmann *et al.*[328] The use of more bulky substrates and nucleophiles gave lower yields as would be expected.

Bergmann *et al*. later found that aryl trichlorocarbinols (R^1 = Ar, R^2 = H) underwent the same reaction under these conditions.[231]

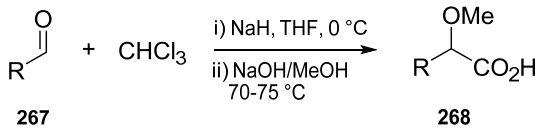
entry	R^1	R^2	R^3	263 yield (%)
a	CH_3	CH_3	Ethyl	68
b	CH_3	CH_3	Butyl	78
c	CH_3	CH_3	*i*-Propyl	44
d	CH_3	CH_3	*i*-Butyl	75
e	CH_3	Ethyl	*i*-Butyl	62
f	- $(CH_2)_5$ -		*i*-Butyl	61

Table 26. Synthesis of α-alkoxy carboxylic acids. Reagents and conditions: KOH (4.0 equiv.), R^3OH, rt to reflux, 3 h.

Reeve *et al*. later reported an improved synthesis of α-methoxyaryl acetic acids **266** using *in situ* trihalocarbinols (Scheme 64).[329-331] By removing the need to isolate the trihalocarbinols, the overall yields were improved and the reaction was successful for a variety of aryl aldehydes with either chloroform or bromoform.



Scheme 64. Synthesis of α-methoxyaryl acetic acids.

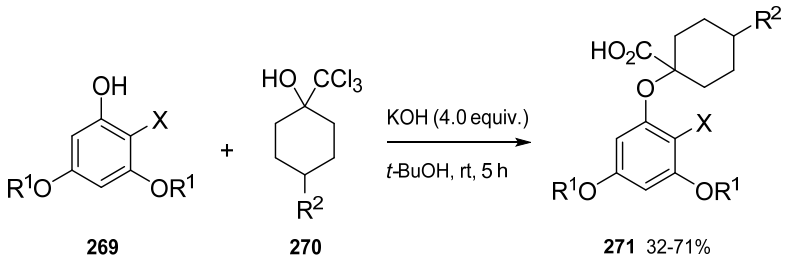


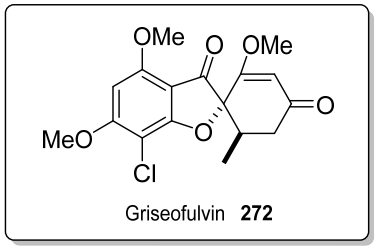
Scheme 65. Synthesis of α-methoxyaliphatic acetic acids. R = alkyl.

Under the conditions shown in scheme 64, aliphatic aldehydes undergo considerable aldol self-condensation. Using an inverse addition technique, Compere *et al*. were able

to suppress aldol side reactions and synthesise a range of α-methoxyaliphatic acetic acids (Scheme 65).[332] The acids **268** were isolated in yields of 24-63% after purification.

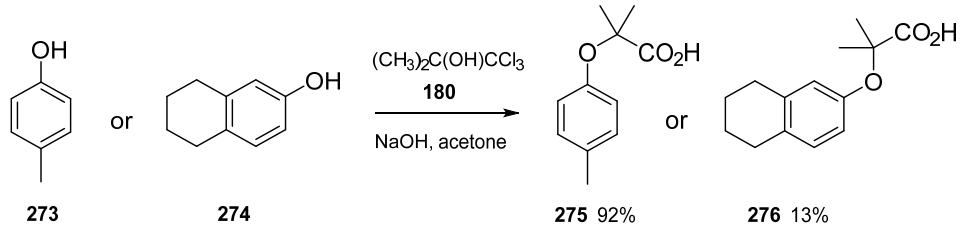
The first example of a Jocic reaction using a phenoxide nucleophile with an isolated trichlorocarbinol appears to be from Korger in 1963 (Scheme 66).[333]





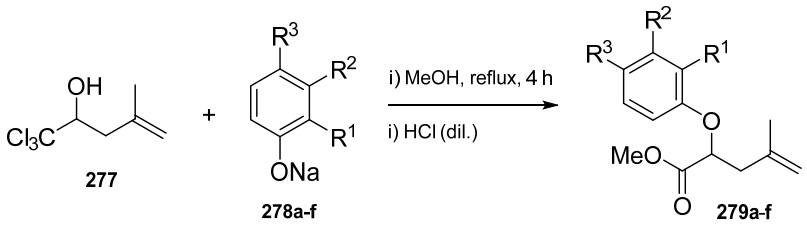
Scheme 66. $R^1 = CH_3, C_2H_5$; R^2 = H, OBn; X = H, Cl, Br.

The reaction was part of a synthesis towards analogues of Griseofulvin **272**.[334] Corey used the reaction of **273** and **274** with "chloretone" **180**, to yield α-phenoxy acids **275** and **276** (Scheme 67).[335]



Scheme 67. Reagents and conditions: phenol (2.0 equiv.), NaOH (8.0 equiv.), acetone, rt, 16 h.

Fechtel *et al.* studied a wider range of phenols in the reaction with trichlorocarbinol **277** (Table 27).[336]

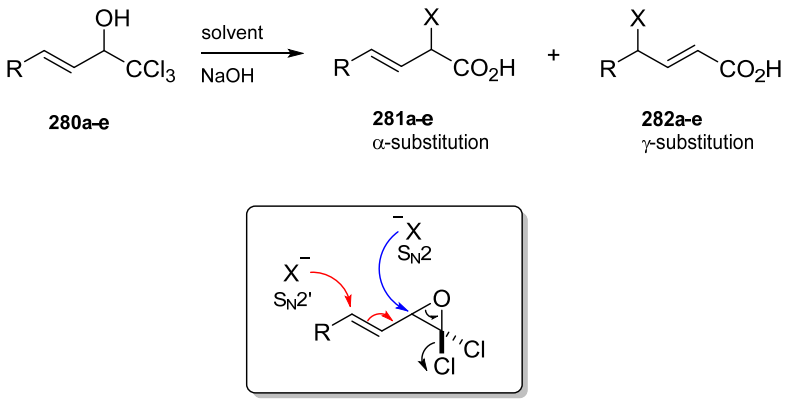


entry	R^1	R^2	R^3	yield (%)	entry	R^1	R^2	R^3	yield (%)
a	H	H	H	41	**d**	CH_3	H	H	28
b	H	H	CH_3	45	**e**	Cl	H	H	19
c	H	CH_3	H	27	**f**	Cl	H	Cl	9

Table 27. Phenoxide **278** was generated *in situ* by the addition of substituted phenol (1.02 equiv.) to sodium in dry methanol.

The authors found that electron-donating groups on the phenol provided higher yields, whilst the opposite was true for electron-withdrawing groups. This is due to the increased or decreased electron density of the phenoxide ion, respectively. It would be expected that methoxide (from the solvent) might compete with phenoxide as a nucleophile. However, an excess of phenol compared to base diminishes the concentration of methoxide ions in solution. In addition to the procedure shown above, Fechtel *et al*. also carried out the reaction in a MeOH/H_2O solvent system to yield the corresponding acids in comparable yields.

Snowden *et al*. developed an approach to α- or γ-substituted enoic acids (Scheme 68).[337] The authors employed several oxygen-based nucelophiles in the Jocic reaction of alkenyl trichlorocarbinols **280**, and a selection of their results are shown in table 28.



Scheme 68. Reaction of alkenyl trichlorocarbinols with various nucleophiles.

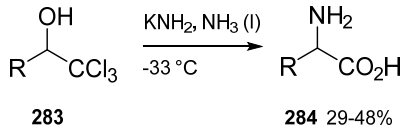
entry	R	solvent	X	281:282	major regioisomer yield (%)
a	*n*-C_5H_{11}	DME/MeOH	OMe	5:1	81
b	*n*-C_5H_{11}	DME/H_2O	OH	1:2	64
c	*n*-C_5H_{11}	Allyl alcohol	OAllyl	> 20:1	93
d	Ph	DME/MeOH	OMe	2.5:1	47
e	Ph	Allyl alcohol	OAllyl	-[a]	-

Table 28. Reagents and conditions: NaOH (6.0 equiv.), 55 °C, 12 h. [a] Not determined.

As expected, methoxide showed preference for the S_N2 pathway (entries **a** and **d**), with reasonable regioselectivity. Allyl alkoxide showed high regioselectivity when R = *n*-C_5H_{11} (entry **c**). Methoxide reacted less selectively when R = Ph (entry **d**), possibly due to conjugation between the aryl and alkene π systems. Unusually, hydroxide showed preference for the S_N2' pathway (entry **d**).

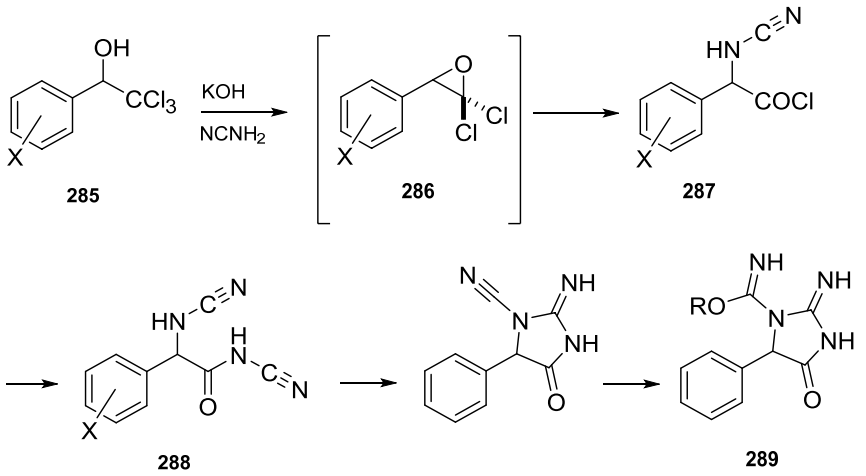
1.15.2 Reactions with Nitrogen-based Nucleophiles

Reeve *et al.* reported the first use of a nitrogen nucleophile in the Jocic reaction (Scheme 69).[338] The product amino acids **284** were obtained only after hydrolysis of the crude mixture. Intermediate α-amino amides and peptides were postulated as intermediates, though these were not positively identified.



Scheme 69. Reagents and conditions: KNH_2 (4.6 equiv.), NH_3 (l), -33 °C, 12 h. R = Et, *i*-Pr, Ph.

When cyanamide ($NCNH_2$) was used as the nucleophile, an unexpected cyclisation reaction occurred to yield cyclic compounds **289** (Scheme 70).[339] Initial ring opening of the *gem*-dichloroepoxide **286**, followed by trapping of the resultant acyl chloride with an additional cyanamide anion, yielded the amino amide **288**. Subsequent cyclisation and formation of a carboximidate (with alcohol from the solvent) led to the cyclic compounds **289** in yields of 22-61%. A significant side reaction is the attack of an alkoxide ion on the dichloroepoxide **286**, leading to the formation of an α-alkoxyaryl acetic acid.

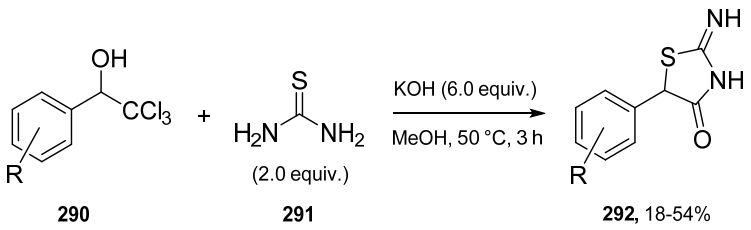


Scheme 70. Reagents and conditions: $NCNH_2$ (2.4 equiv.), KOH (5.9 equiv.), ROH, rt, overnight. R = CH_3, C_2H_5, *n*-Pr, *n*-Bu; X = H, *p*-Cl, *p*-OMe.

1.15.3 Reactions with Sulfur-based Nucleophiles

Reeve studied thiourea as an example of the Jocic reaction with a sulfur nucleophile (Scheme 71).[340] Although thiourea is potentially an ambidentate ligand, no evidence was observed for attack by nitrogen on the *gem*-dichloroepoxide. Additionally, no α-

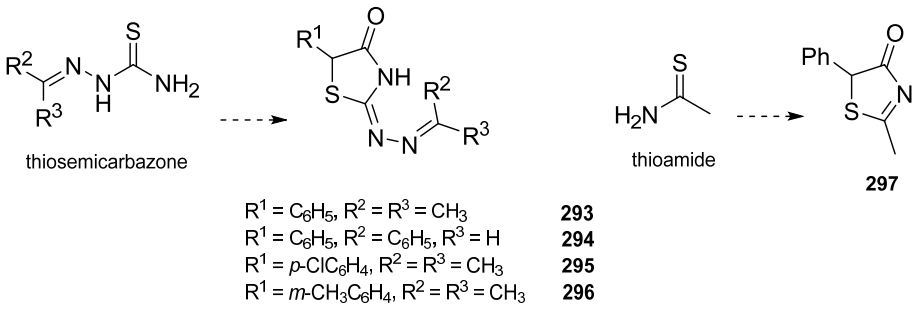
methoxyaryl acetic acids were observed, indicating that the sulfur nucleophile outcompetes any methoxide from the solvent.



290 **291** **292,** 18-54%

Scheme 71. Jocic reaction of thiourea with aryltrichlorocarbinols. R = H, 3,4-dichloro, *p*-OMe.

The use of thiosemicarbazones or thioamide gave the heterocyclic compounds **293-296** and **297** (Scheme 72) respectively, by an analogous mechanism.[341] Further bifunctional reagents containing a nucleophilic sulfur atom were studied by Reeve and Coley III.[342] Blanchett and Zhu later improved the yield of the reaction with substituted thioureas by using DME/H_2O as the solvent.[343]

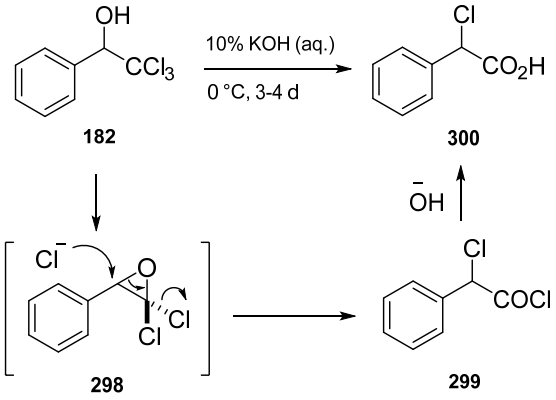


Scheme 72. Additional reactions with sulfur nucleophiles.

1.15.4 Reactions with Halide Nucleophiles

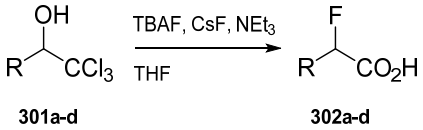
The first example of a reaction of this type was in the original publication from Jocic (Scheme 73), where he postulated chloride to be the nucleophile in the ring opening of epoxide **298**.[221, 222] Reeve has suggested that this reaction may go *via* different intermediates from the generally accepted *gem*-dichloroepoxide.[344, 345] However, this is not consistent with the stereospecificity of the reaction (see later) or with X-ray crystallography data.[327] At temperatures above 0 °C considerable hydrolysis of the α-

chlorocarboxylic acid **300** occurs, to yield the α-hydroxy-substituted acid. When tertiary trichlorocarbinols are used, the elimination of $CHCl_3$ from the trichlorocarbinol **182** becomes a significant reaction pathway.



Scheme 73. The original Jocic reaction.

Oliver *et al*. prepared α-fluoro carboxylic acids by treatment of trichlorocarbinols with tetrabutylammonium fluoride (TBAF) and cesium fluoride (Table 29).[346] Good yields were obtained, although only four substrates were examined and all four were structurally very similar. The reaction failed when methanol was used as the solvent due to the formation of the α-methoxy acid. Oliver *et al*. later used enantiomerically enriched trichlorocarbinols to obtain α-fluoro carboxylic acids in > 92% *e.e.* but with α-chloro carboxylic acid side products.[347]

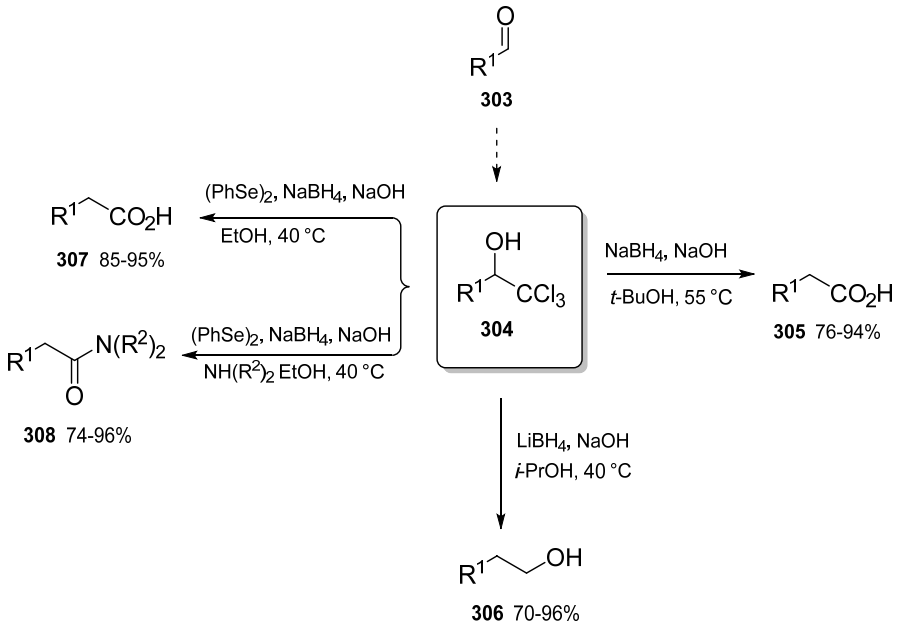


entry	R	302 yield (%)	entry	R	302 yield (%)
a	C_9H_{19}	100	**c**	$C_8H_{17}CC(CH_2)_8$	81
b	$C_{16}H_{31}$	81	**d**	$C_2H_5CC(CH_2)_8$	76

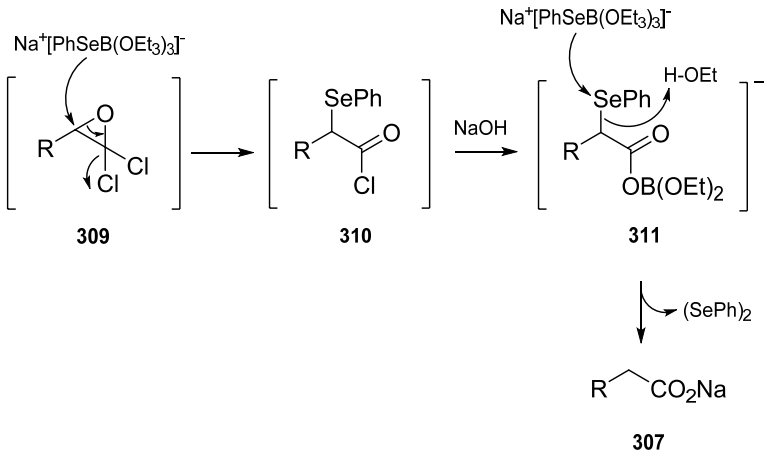
Table 29. Reagents and conditions: TBAF (12 equiv.), CsF (14 equiv.), NEt_3 (7.2 equiv.), THF, reflux, 2 h.

1.15.5 Reactions with Hydride Nucelophiles

Snowden *et al*. developed several one-carbon homologation reactions, starting from trichlorocarbinols **304**, employing hydride or selenide as the nucleophile (Scheme 74).[348-350] Subtle differences in the reaction conditions provided either the homologated carboxylic acid **305**, or the alcohol **306**. The acid product is a result of hydrolysis of the intermediate acid chloride, whilst the alcohol results from faster reduction of the acid chloride by $LiBH_4$. A proposed mechanism for the selenium reaction is shown in scheme 75. When amines are added to the reaction mixture they trap the intermediate acid chloride (**310**) to yield amides **308**.



Scheme 74. Various homologation procedures developed by Snowden *et al*. R^1 = alkyl, alkenyl, aryl; $NH(R^2)_2 = NH_2$, benzylamine, morpholine.

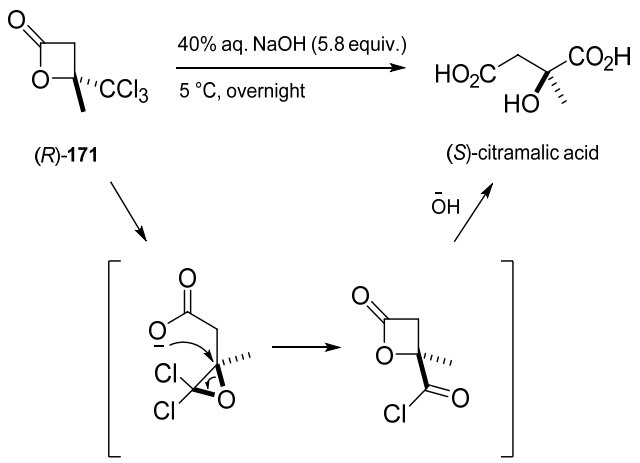


Scheme 75. Proposed conversion of dichloroepoxide **309** to carboxylate **307** using sodium phenylseleno(triethyl)borate complex.

1.16 Jocic Reactions with Enantiomerically Enriched Trichlorocarbinols

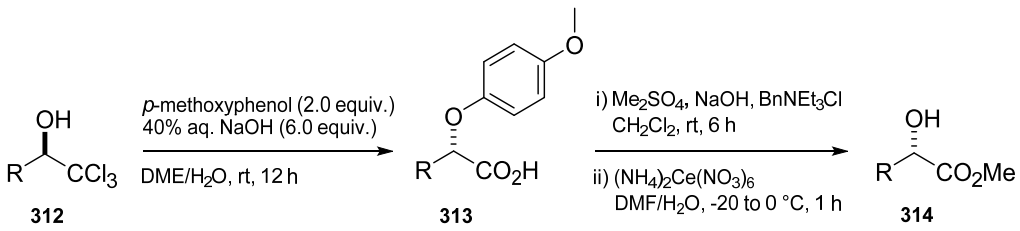
1.16.1 Reactions with Oxygen-Based Nucleophiles

The highly stereospecific nature of the Jocic reaction has made it an attractive synthetic tool, if the starting trichlorocarbinols are obtainable in high stereochemical purity and racemisation is minimised. Wynberg *et al*. synthesised (*R*)- and (*S*)-citramalic acid *via* the ring opening and *intramolecular* Jocic reaction of lactone (*R*)-**171** (Scheme 76).[351] (*S*)-Citramalic acid was obtained without racemisation and in 96% yield. The (*R*)-enantiomer was obtained using the same procedure but starting from (*S*)-lactone.



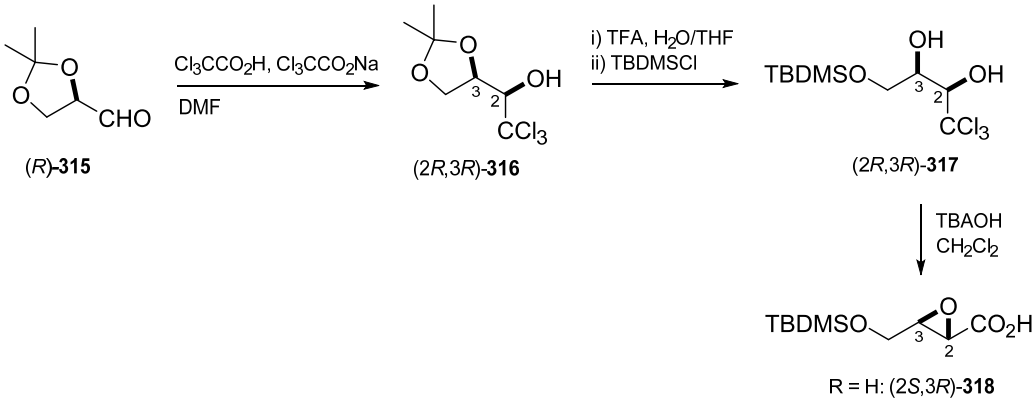
Scheme 76. Stereospecific synthesis of (*S*)-citramalic acid.

Corey and Link employed a *p*-methoxyphenol nucleophile in the Jocic reaction with enantiomerically enriched trichlorocarbinols **312** (Scheme 77).[352] The trichlorocarbinols were synthesised in 92-98% *e.e.* by the previously reported CBS reduction.[298, 301] Only for R = $C_6H_5(CH_2)_2$ was experimental data provided, with the authors claiming "optical purity" for the α-hydroxy methyl ester **314** without providing additional evidence.



Scheme 77. Stereoselective synthesis of α-hydroxy esters. R = *n*-pentyl, $C_6H_5(CH_2)_2$, cyclohexyl, *t*-butyl.

It has been shown previously that an appropriately placed hydroxyl group will act as a nucleophile in an intramolecular Jocic reaction.[336] Oliver and Schmidt used this strategy in the synthesis of an enantiomerically enriched epoxyacid (**318**, Scheme 78).[353]

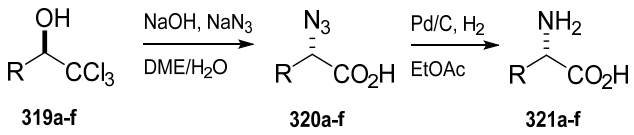


Scheme 78. Synthesis of an epoxycarboxylic acid *via* an intramolecular Jocic reaction. TBAOH = tetrabutylammonium hydroxide.

Alcohol **316** was obtained as a 63:27 ratio of diastereoisomers, of which the (2*R*,3*R*)-isomer was obtained directly by recrystallisation. The Jocic reaction of diol **317** to epoxide **318** proceeded stereospecifically with inversion, and none of the (2*R*,3*R*) diastereoisomer was detected. The biphasic conditions employed in this step helped to prevent racemisation of the C-2 centre.

1.16.2 Reactions with Nitrogen-Based Nucleophiles

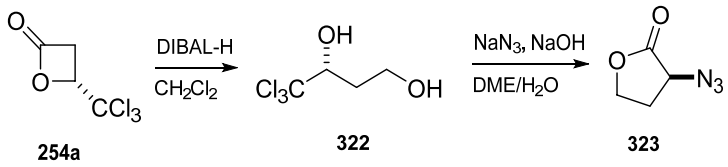
Corey and Link reported the convenient, enantioselective synthesis of α-amino acids (Table 30).[302] The amino acids **321** were obtained in high enantiomeric excess after reduction. The success of the reaction (and absence of racemisation) under these homogeneous conditions probably lies in the strong nucleophicity of azide.



entry	R	320 yield (%)	321 yield (%)
a	*n*-Pentyl	89	94
b	$C_6H_5(CH_2)_2$	91	92
c	*p*-$C_6H_5C_6H_4CH_2$	82	98
d	2-Naphthylmethyl	84	88
e	Cyclohexyl	89	92
f	*t*-Butyl	80	94

Table 30. Reagents and conditions: NaOH (4.0 equiv.), NaN_3 (2.0 equiv.), DME/H_2O, rt, 12 h; 10% Pd/C (25 wt%), H_2, EtOAc, rt, 12 h.

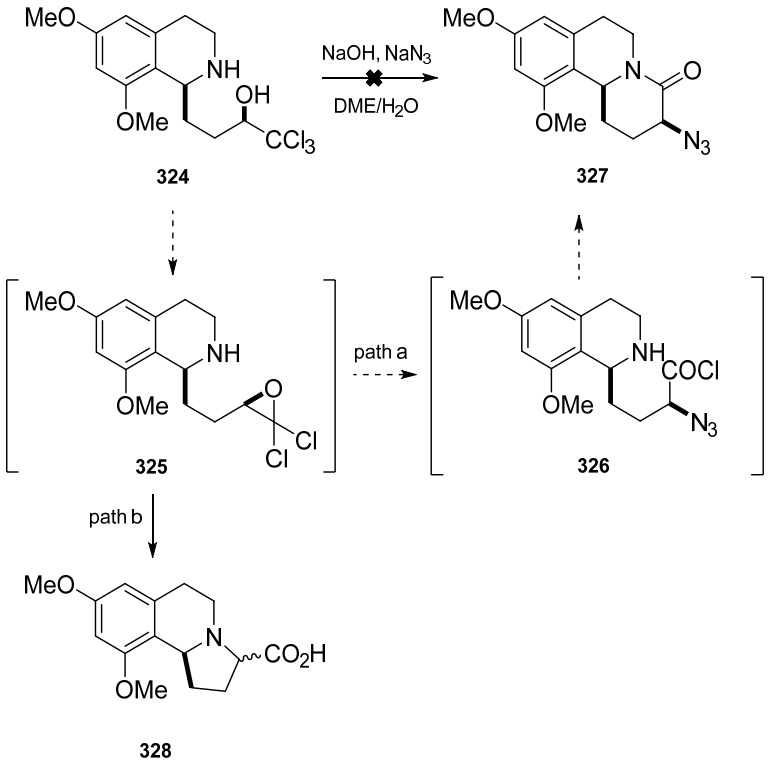
Romo *et al*. used Corey's conditions as part of the synthesis of an α-azido γ-lactone (Scheme 79).[354-356] Ring opening of the enantiomerically pure lactone **254a** by the procedure of Fujisawa yielded diol **322** with no loss of stereochemistry.[357, 358] Treatment with NaOH/NaN_3 then gave the lactone **323**, after gentle heating in methanol to promote cyclisation.



Scheme 79. Stereospecific synthesis of an α-azido γ-lactone. Reagents and conditions: DIBAL (1.0 equiv.), CH_2Cl_2, rt, 10 h; NaOH (4.0 equiv.), NaN_3 (2.0 equiv.), DME/H_2O, rt, 12 h.

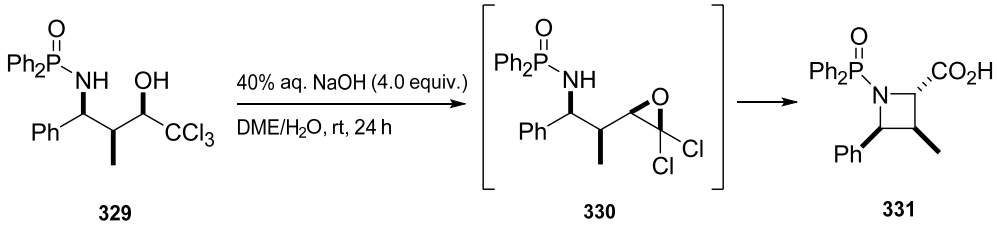
As part of a synthesis towards Schulzeines B and C, Romo and Liu attempted to use similar methodology to generate intermediate **327** (Scheme 80).[359] Unexpectedly, ring-opening of dichloroepoxide **325** by azide (path a) was not observed. Instead, intramolecular attack by the piperidine nitrogen atom (path b) occurred and

pyrrolidine **328** was formed as a 6:1 mixture of diastereoisomers. Boc protection of the piperidine N atom prior to the Jocic reaction yielded the desired azido compound **327**.



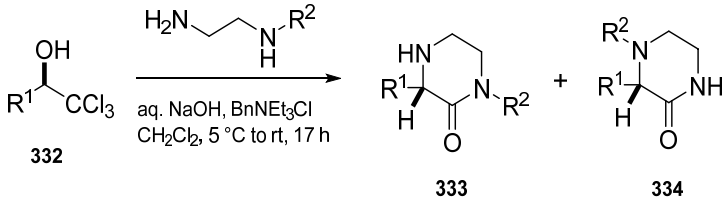
Scheme 80. Attempted synthesis of δ-lactam **327**.

Shibasaki *et al*. described the diastereoselective synthesis of substituted azetidine-2-carboxylic acids (Scheme 81).[360] The trichlorocarbinol **329** was obtained in high *d.e.* by reduction of the trichloroketone precursor. No epimerisation of the C-2 chiral centre during the Jocic reaction was observed.



Scheme 81. Synthesis of a 3,4-*syn*-disubstituted azetidine-2-carboxylic acid.

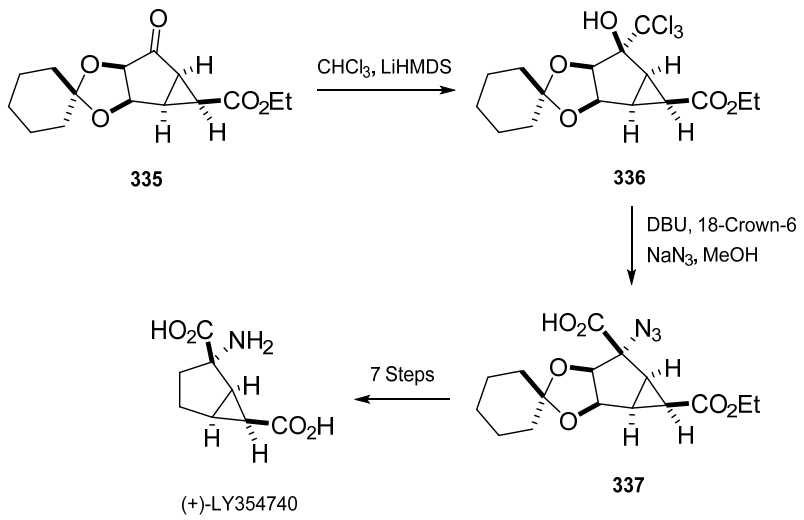
Perryman *et al*. have used both symmetrical and unsymmetrical diamines in Jocic-type reactions with enantiomerically enriched trichlorocarbinols **332** (Scheme 82).[361, 362] Generally, as the size of R^2 on the secondary amine increases, the formation of 1-substituted piperazin-2-ones (**333**) was favoured. This may be due to preferential attack of the less sterically hindered amine when opening the dichloroepoxide. For all the substrates examined high *e.e.* values were obtained; however, under homogenous reaction conditions (aq. NaOH, MeOH) the *e.e.* of the products was lowered. Racemic reactions of this type had been previously reported by Lai, although with lower regioselectivity.[363, 364]



Scheme 82. Synthesis of piperazin-2-ones. $R^1 = (CH_2)_2Ph$, R^2 = alkyl, aryl.

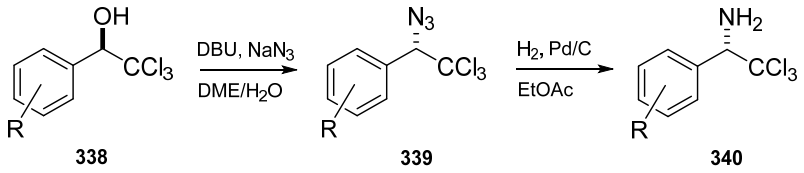
Dominguez *et al*. reported so-called "modified Corey-Link" conditions in the synthesis of (+)-LY354740, a potent agonist for the group 2 metabotropic gluatamate receptors (mGluRs)[365] (Scheme 83).[366, 367] (+)-LY354740 showed efficacy in clinical studies for the treatment of generalised anxiety disorder (GAD).[368] Alcohol **336** was obtained in enantiomerically pure form due to attack of the trichloromethyl anion on the less sterically hindered face. When Corey's conditions were applied the desired α-azido acid **337** was contaminated with the diacid, which made purification difficult. In order to avoid this partial ester hydrolysis, anhydrous conditions using the organic base DBU were employed. Under these milder conditions the reaction proceeded smoothly with complete inversion. Notably, the Strecker reaction gave rise to the opposite stereochemistry at this quaternary centre.[369] This "modified Corey-Link"

methodology has found considerable application, particularly in sugar chemistry.[370-372]



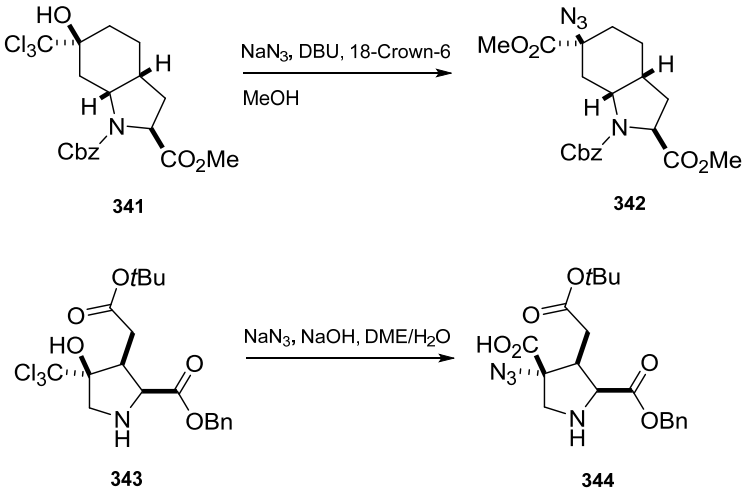
Scheme 83. Synthesis of (+)-LY354740.

Aitken *et al.* applied similar modified conditions in the synthesis of α-aryl glycines (Scheme 84).[373] The use of Corey and Link's original procedure resulted in complete racemisation of **339**. However, by using DBU as the base, the (*S*)-aryl glycines **340** were prepared in overall yields of 40-62% and > 97% *e.e.* in all examples.



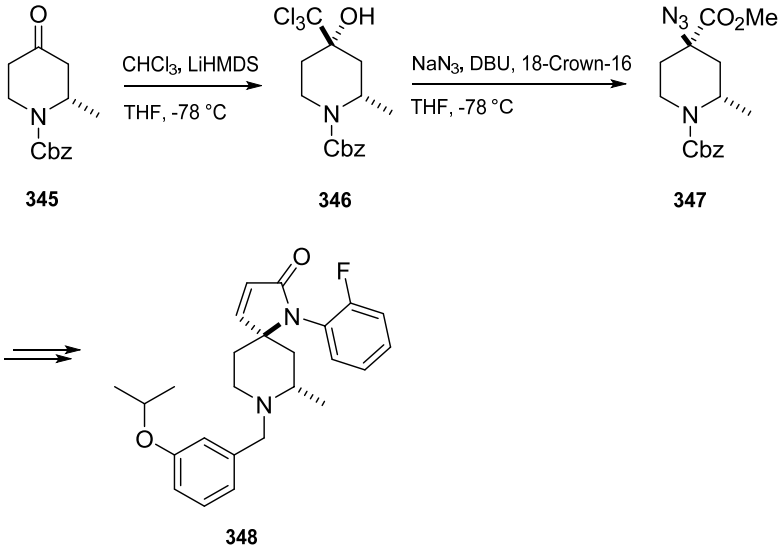
Scheme 84. Reagents and conditions: DBU (1.0 equiv.), NaN_3 (2.0 equiv.), DME/H_2O, rt, 24 h.

Schafmeister *et al.* employed both modified and original Corey-Link conditions during the separate syntheses of **342** and **344**, precusors to *bis*-amino acid monomers (Scheme 85).[374, 375]

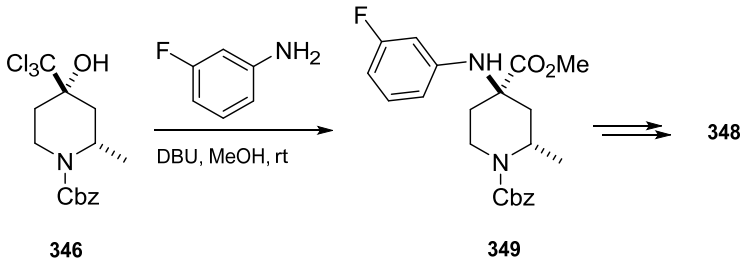


Scheme 85. Synthesis of two *bis*-amino acid monomer precursors.

Lee *et al.* synthesised α-azido acid **347** using modified Corey-Link conditions (Scheme 86),[376] as part of efforts to identify a novel series of β-site amyloid precursor protein cleaving enzyme (BACE-1) inhibitors.[377, 378] During scale-up studies it was found that a Jocic reaction with 3-fluoroaniline provided a better alternative to using azides (Scheme 87).[379, 380]



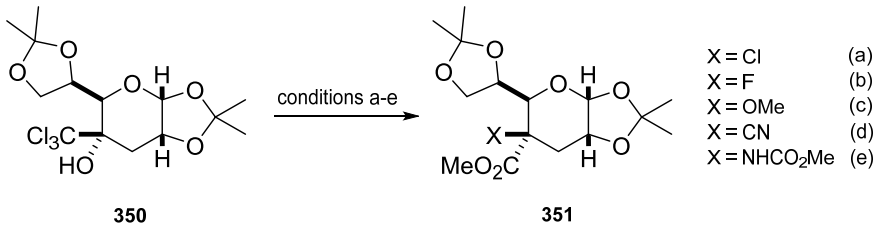
Scheme 86. Discovery synthesis of lead compound **348**.



Scheme 87. Optimised synthesis for large-scale production.

1.16.3 Reactions with Other Nucleophiles

Stick *et al*. used a number of nucleophiles in the Jocic reaction with a sugar-derived trichlorocarbinol (Scheme 88).[327, 381]



Scheme 88. Conditions: a) DBU, MeOH, 83%; b) CsF, DBU, MeOH, 85%; c) NaOMe, MeOH, 54%; d) NaCN, DBU, MeOH, 80%; e) KOCN, DBU, MeOH, 50%.

1.17 Bargellini Reactions

Like the Jocic reaction, what has become known as the Bargellini reaction was discovered in the early 1900s and involves a *gem*-dichloroepoxide as a key intermediate. The difference between the two lies in the isolation of a trichlorocarbinol; in the Jocic reaction these are typically synthesised or purchased initially and then reacted further with nucleophiles, whilst in a Bargellini reaction they are generated *in situ* (Scheme 43). The one-pot, operationally simple nature of these reactions have made them attractive to researchers in the pharmaceutical industry. Examples of such target molecules are shown in figure 5.[382-389]

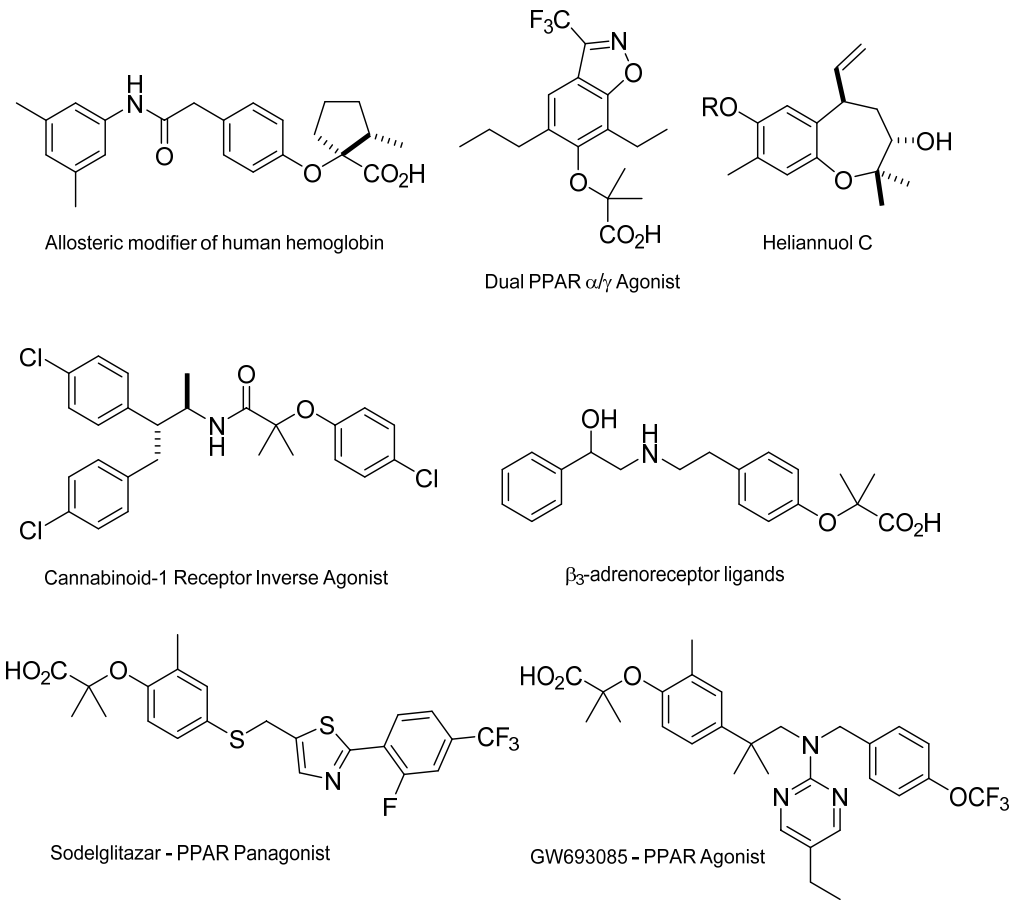
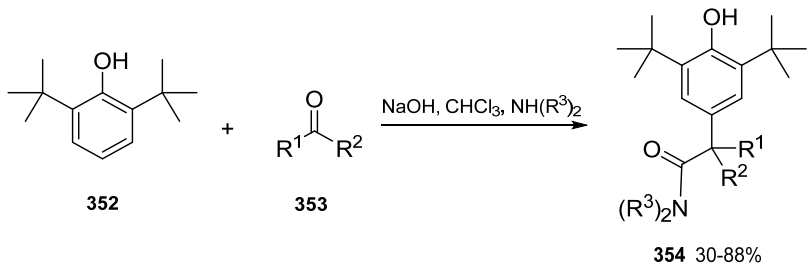


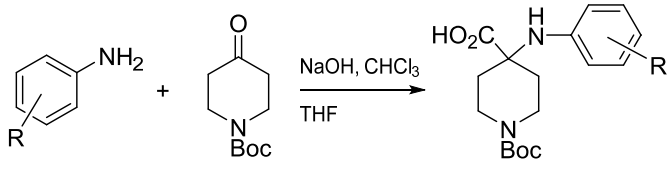
Figure 5. A selection of target compounds which use a Bargellini reaction to install the α-disubstituted carboxylic acid motif.

Lai reported an interesting variation on the usual Bargellini reaction, using a hindered phenol as the nucleophile (Scheme 89).[390] Due to the hindered nature of the phenol, the dichloroepoxide intermediate is attacked by the *para* carbon of the phenol. The acid chloride was trapped by a range of secondary amines to yield amides **354**.



Scheme 89. Reagents and conditions: ketone (8.0 equiv.), $CHCl_3$ (1.3 equiv.), NaOH (4.5 equiv.), 10 °C, 20 h. R^1/R^2 = alkyl, cycloalkyl; R^3 = alkyl.

Classically, a phenol is used as the nucleophile in the Bargellini reaction. Butcher and Hurst demonstrated that anilines work well in place of phenol (Table 31). Better yields were obtained with the more electron-rich anilines (entries **a** and **e**), which mirrors the reactivity of phenols as expected. In addition to the nucleophiles shown in table 31, Butcher and Hurst also used thiophenol (71% yield), 2-aminopyridine (72% yield) and 1*H*-pyrazole (56% yield). KF on alumina was reported as an alternative base by Myrboh and Rohman.[391] Saidi and Aryanasab employed a wider range of thiol nucleophiles, including the first reported use of dithiocarbamic acid as a nucleophile.[392]



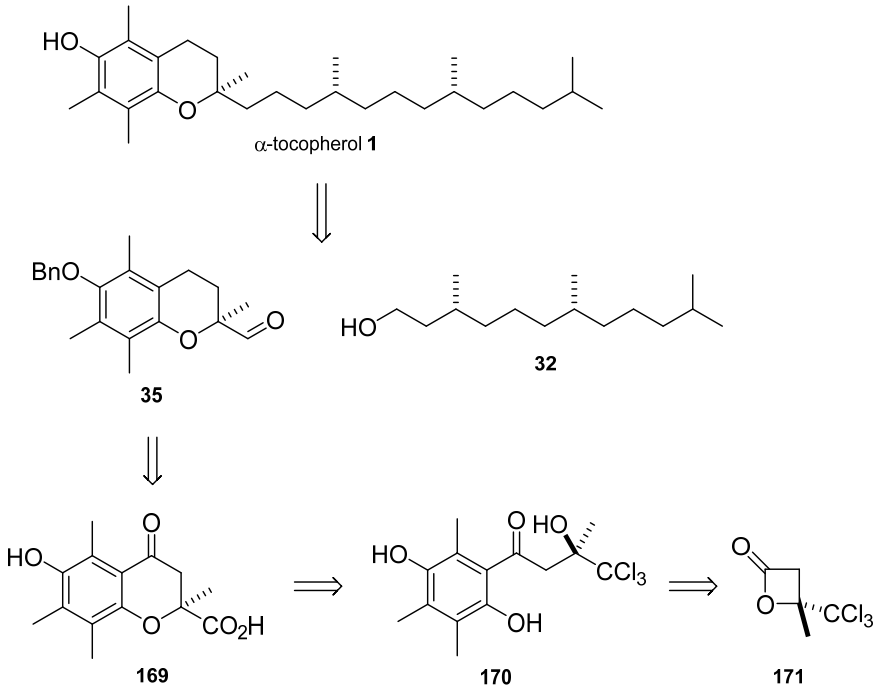
355a-e **356** **357a-e**

entry	R	357 yield (%)
a	H	70
b	*p*-Br	56
c	*m*-Br	67
d	*p*-CO_2Me	56
e	*m*-OMe	99

Table 31. Reagents and conditions: ketone (3.0 equiv.), $CHCl_3$ (5.0 equiv.), NaOH (5.0 equiv.), THF, rt, 18 h.

Chapter 2: The Total Synthesis of Vitamin E

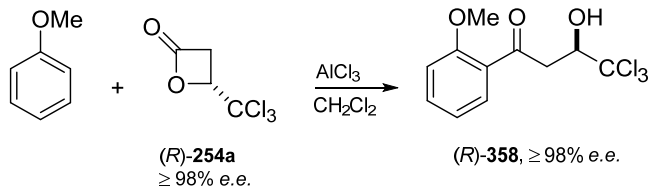
The preliminary disconnections for the synthesis proposal are shown in scheme 90. The disconnection of vitamin E to the chromane aldehyde **35** and (*R*,*R*)-hexahydrofarnesol **32** is well documented in the literature.[166, 167, 169-173, 196, 393, 394] We imagined that we could ultimately synthesise the key aldehyde *via* the intramolecular Jocic reaction of phenol **170**. Using this strategy, all four tocopherol analogues should be accessible.



Scheme 90. Disconnections for the synthesis of vitamin E. R^1, R^2, R^3 = CH_3 or H.

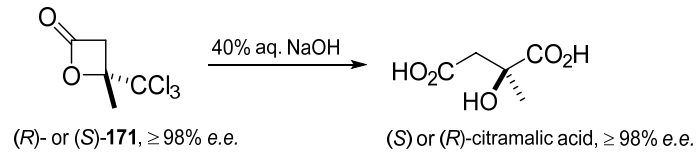
2.1 Synthesis of Model Compounds

We initially anticipated that the β-keto trichlorocarbinol **170** should be accessible from the ring-opening of Wynberg lactone (*R*)-**171**. The Friedel-Crafts ring opening of a related lactone (*R*)-**254a** was reported to take place with no change in the enantiomer composition (Scheme 91).[395]



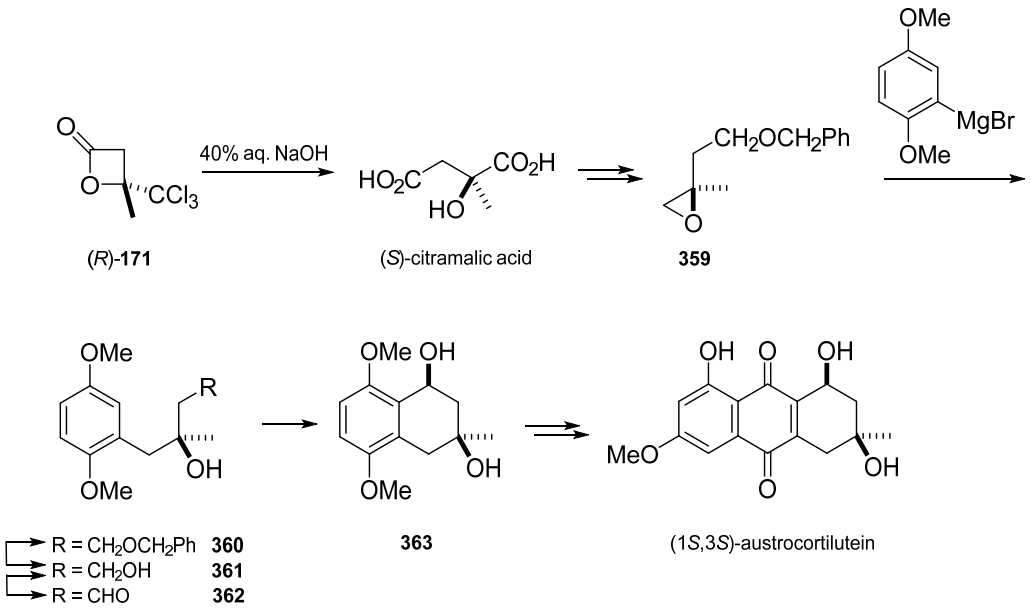
Scheme 91. Friedel-Crafts acylation of anisole with trichlorolactone (*R*)-**254a**.

The ring opening of lactone **171** by this method has not been reported in the literature. In contrast to the 4-monosubstituted derivative **254a**, reports on the use of lactone **171** in synthesis are scarce. Of only two reports in the literature, both involve the basic hydrolysis of (*R*)- or (*S*)-**171** to yield (*R*)- or (*S*)-citramalic acid respectively (Scheme 92).[351]



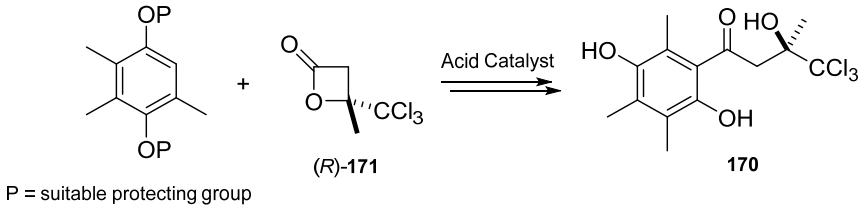
Scheme 92. Synthesis of (*S*)-citramalic acid by Wynberg and Staring.

Gill *et al*. used lactone **171** as a source of citramalic acid for their synthesis of (1*S*,3*S*)-Austrocortilutein (Scheme 93).[396] Using (*S*)-**171** allowed the synthesis of the other (1*R*,2*R*) enantiomer.



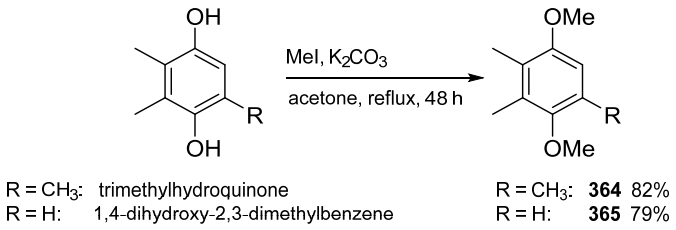
Scheme 93. Synthesis of (1*S*,3*S*)-austrocortilutein.

We anticipated that lactone **171** could be ring opened by a suitable 1,4-dimethoxybenzene compound, to ultimately yield phenol **170** (Scheme 94).

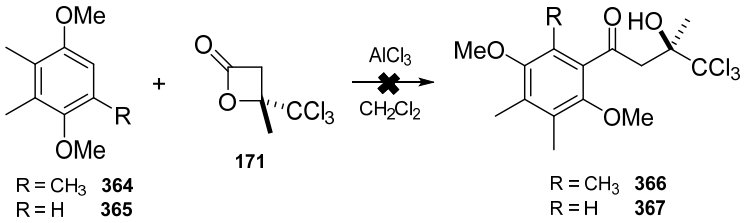


Scheme 94. Proposed Friedel-Crafts acylation of protected hydroquinones.

Protecting groups were needed both to prevent *O*-acylation and to stabilise the hydroquinone against oxidation during the reaction. Methyl ethers were expected to survive the strongly acidic conditions, although they can require strong reagents for deprotection. Accordingly, 2,3,5-trimethyldimethoxy benzene **364** and 2,3-dimethyldimethoxy benzene **365** were synthesised using a literature procedure[397] (Scheme 95) and subjected to the Friedel-Crafts conditions reported by Fujisawa *et al*. (Scheme 96).[395]

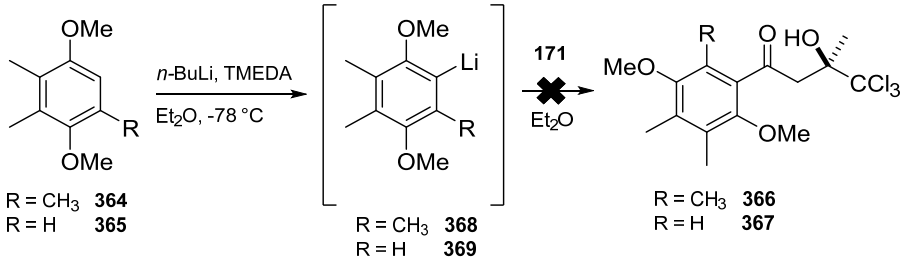


Scheme 95. Methylation of hydroquinones.



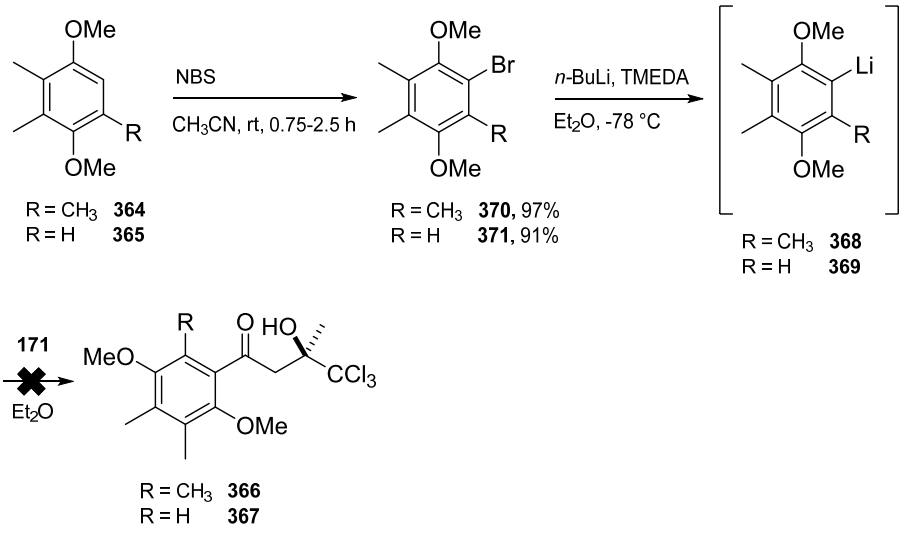
Scheme 96. Attempted ring opening of lactone **171** under Friedel-Crafts conditions.

Unfortunately, neither trichlorocarbinol **366** nor **367** were observed under these conditions even at increased reaction temperatures and times. Seeking an alternative procedure, we attempted to synthesise lithiated derivatives of **364** and **365** *in situ*, and treat these with lactone **171** (Scheme 97).



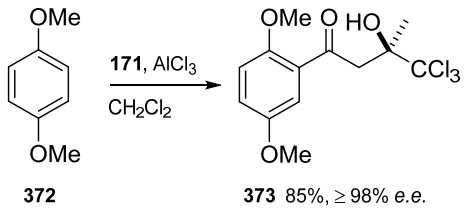
Scheme 97. Attempted ring opening of lactone **171** by lithiation of arenes **364** and **365**. TMEDA = tetramethyl ethylenediamine.

This reaction yielded unchanged starting materials, although quenching the reaction with D_2O showed complete deuterium incorporation, suggesting that it was the ring-opening step which was failing. The use of brominated arenes **370** or **371** in a lithium exchange reaction also failed (Scheme 98).



Scheme 98. Attempted ring opening of lactone **171** by the lithium exchange of bromobenzenes. NBS = *N*-bromosuccinimide.

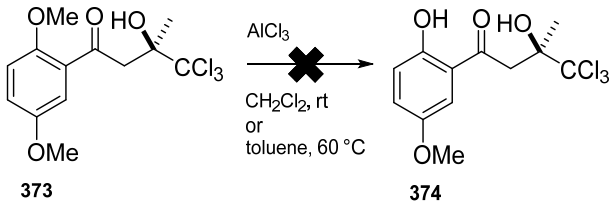
Since the reactions were probably failing on steric grounds, commercially available 1,4-dimethoxybenzene **372** was used as a less challenging model substrate. Thus, treatment of **372** with $AlCl_3$ and **171** in CH_2Cl_2 provided the trichlorocarbinol **373** in good yield and with ≥ 98% *e.e.* (Scheme 99). The enantiomeric excess of trichlorocarbinol **373** was measured by comparison with a racemic substrate (see later).



Scheme 99. Successful ring opening of lactone **171**.

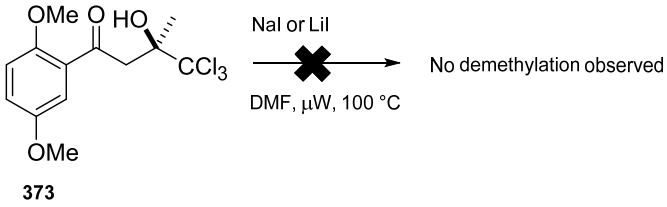
Our proposal for an intramolecular Jocic reaction required that the 2'-methoxy group be deprotected, and a report in the literature from Du *et al.* suggested that this could be carried out selectively due to the *ortho*-acyl substitution.[398] However, given that Du *et al*. used $AlCl_3$ to accomplish this transformation, and that no demethylated products were observed in the reaction of **372** to **373**, it seemed unlikely that this reaction would

be successful. Nevertheless, it was attempted (1.5 equiv. $AlCl_3$, CH_2Cl_2, rt) and found that the starting materials remained unchanged. Using toluene as the solvent to increase the reaction temperature resulted in decomposition of the substrate at temperatures above 60 °C (Scheme 100).



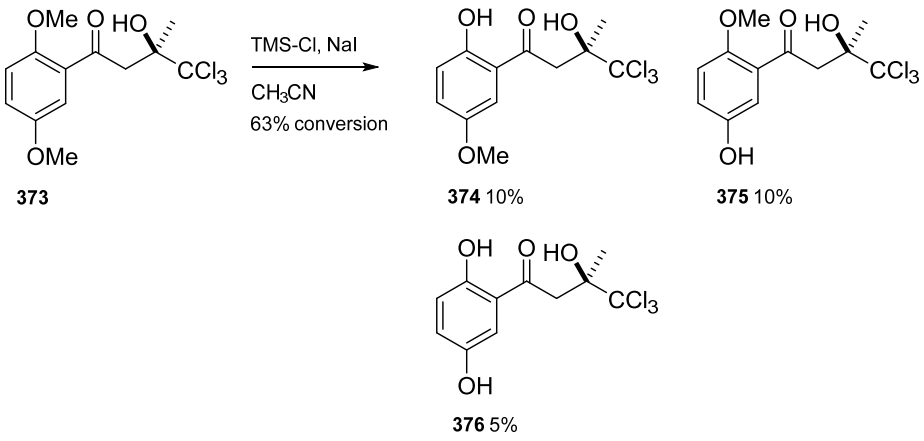
Scheme 100. Failed *ortho*-selective demethylation reaction.

Using NaI or LiI in DMF under microwave irradiation[399] also failed to yield any phenol products (Scheme 101).



Scheme 101. Unsuccessful demethylation using NaI or LiI.

More promisingly, a TMS-Cl/NaI system developed by Olah *et al.*[400] yielded a mixture of both partially and completely demethylated compounds (Scheme 102). The ratio of [**374**:**375**:**376**] was approximately 1:0.6:0.6 as determined from the ^{1}H NMR spectrum of the crude mixture. Even though this reaction displayed poor selectivity for the *ortho* methoxy group, we decided to optimise the reaction conditions for the synthesis of the hydroquinone **376** since separation of all three compounds by column chromatography was difficult.



373

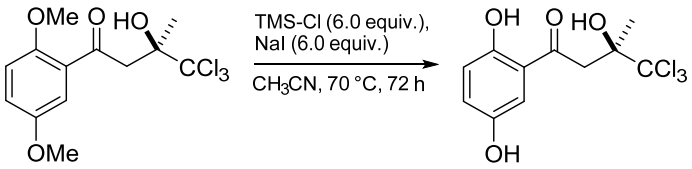
374 10%

375 10%

376 5%

Scheme 102. Unoptimised demethylation of methyl ether **373**.

Unfortunately, the highest yield obtained for this reaction was 33% (Scheme 103). This may be partly because hydroquinone **376** is readily oxidised – the compound was also unstable towards column chromatography.

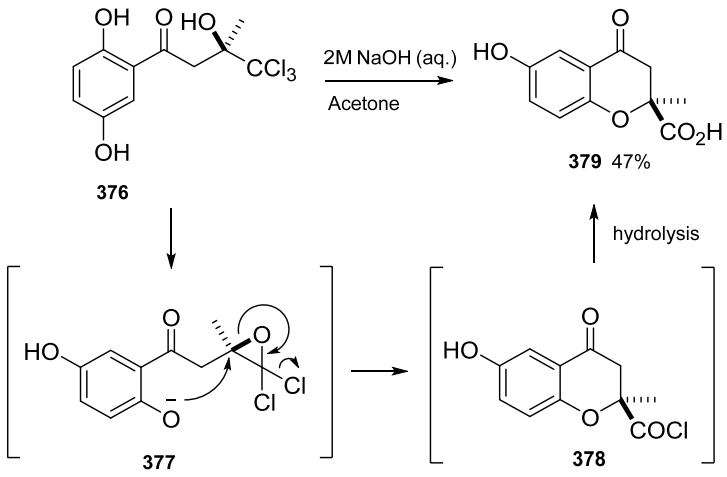


373

376 33%

Scheme 103. Optimised demethylation protocol.

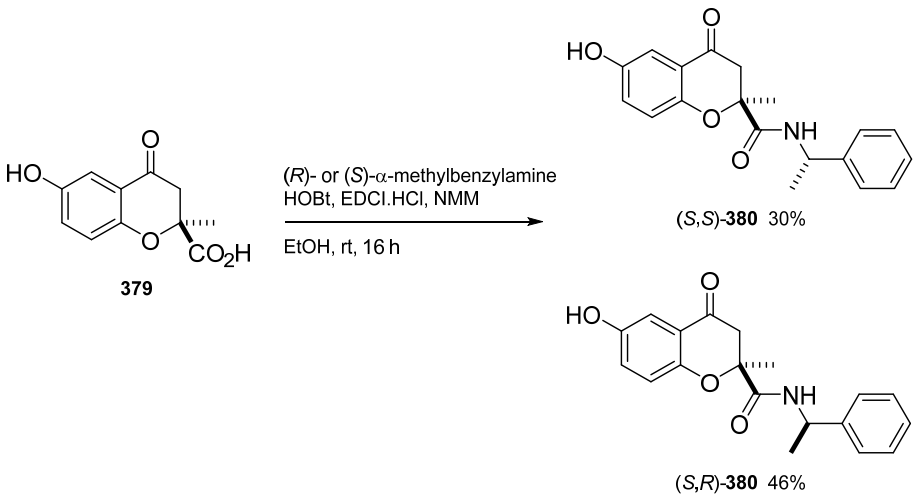
Despite the low yields obtained from the demethylation step, sufficient material could be brought through to test the key step; the intramolecular Jocic reaction. Thus, treatment of hydroquinone **376** with four equivalents of 2M NaOH (aq.) yielded the 4-oxochromane-2-carboxylic acid **379** (Scheme 104). The reaction was carried out under nitrogen and in a sparged solution to minimise oxidation of the hydroquinone. Initially, the work up consisted of pH adjustment to 2-3 followed by extraction with EtOAc. Cleaner product could be obtained by first washing the alkaline solution with organic solvent to remove organic soluble byproducts, before lowering the pH to release the compound.



Scheme 104. Intramolecular Jocic reaction mechanism.

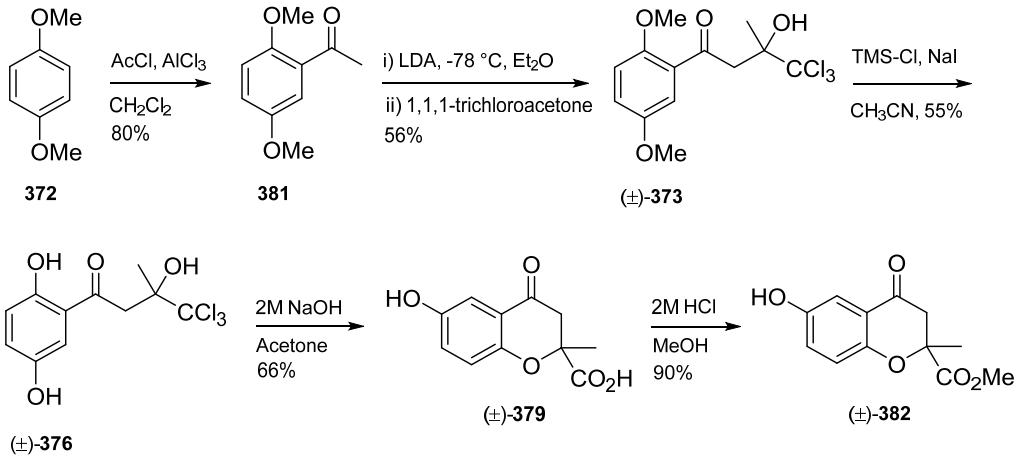
The accepted mechanism for the conversion of **376** into **379** is shown in scheme 104. Contrary to Reeve's claim that tertiary trichlorocarbinols cannot take part in the Jocic reaction,[345] reasonable yields of the α-disubstituted carboxylic acid **379** could be obtained. No evidence of ring opening of the intermediate epoxide **377** by either chloride or another molecule of **376** was observed.

We first attempted to measure the enantiomeric excess of the C-2 centre by coupling carboxylic acid **379** to (*S*)- and (*R*)-α-methylbenzylamine (Scheme 105). Unfortunately, the C*H*$_3$CH doublets in (*S*,*S*)- and (*S*,*R*)-**380** were not different enough in chemical shift to be useful as a measure of the diastereomeric ratio. The CH_3 singlet also did not show enough of a difference in chemical shift in either diastereoisomer.



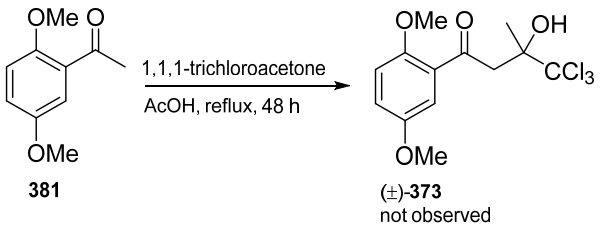
Scheme 105. Synthesis of diastereomeric amides **380**.

A racemic synthesis of **379** was planned (Scheme 106), which would also allow for an *e.e.* measurement of compound **373**.



Scheme 106. Synthesis of 4-oxo-chromane (±)-**382**.

The aldol condensation of acetophenone **381** with 1,1,1-trichloroacetone proceeded with moderate yields, and no elimination product was observed. An attempted acid catalysed aldol reaction failed (Scheme 107).



Scheme 107. Failed acid-catalysed aldol condensation.

The demethylation of trichlorocarbinol (±)-**373** proceeded with slightly greater yield than for the enantiomerically enriched compound, and subsequent treatment with 2M NaOH (aq.) in acetone yielded the carboxylic acid (±)-**379**. Chiral HPLC analysis was performed on the ester (±)-**382**.

Chiral HPLC analysis showed no loss of stereochemistry during the ring-opening reaction of lactone **171**, as hoped (Figure 6). The intramolecular Jocic reaction also proceeded without racemisation (Figure 7). This complete lack of racemisation is a consequence of the intramolecular ring opening of the intermediate dichloroepoxide **377** taking place in strict S_N2 fashion. Additionally, neither acid chloride **378** nor the acetate product **379** are enolisable.

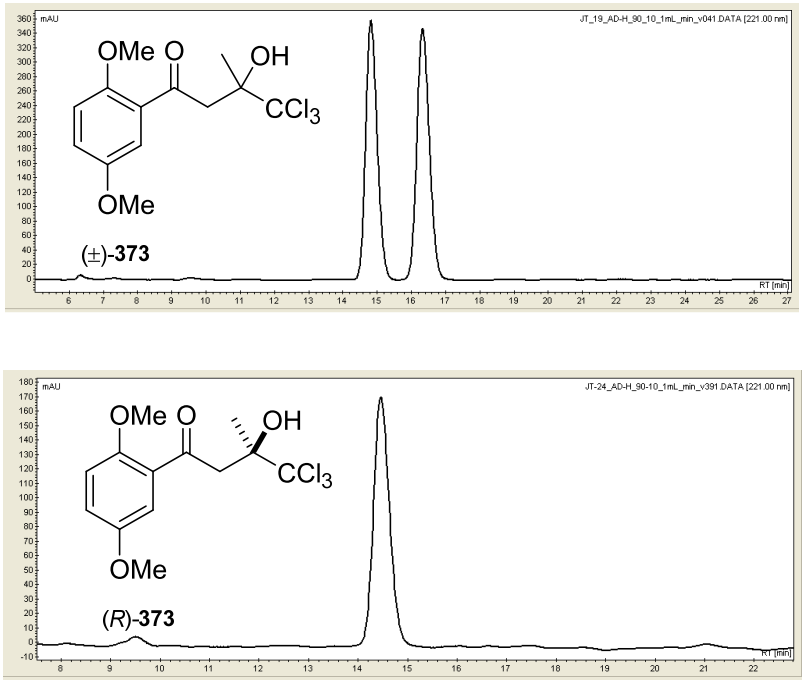


Figure 6. Top: HPLC trace of (±)-**373**. Bottom: HPLC trace of (*R*)-**373**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 90 : 10, 1 mL/min, 221 nm, (*R*) isomer 14.81 min, (*S*) isomer 16.33 min.

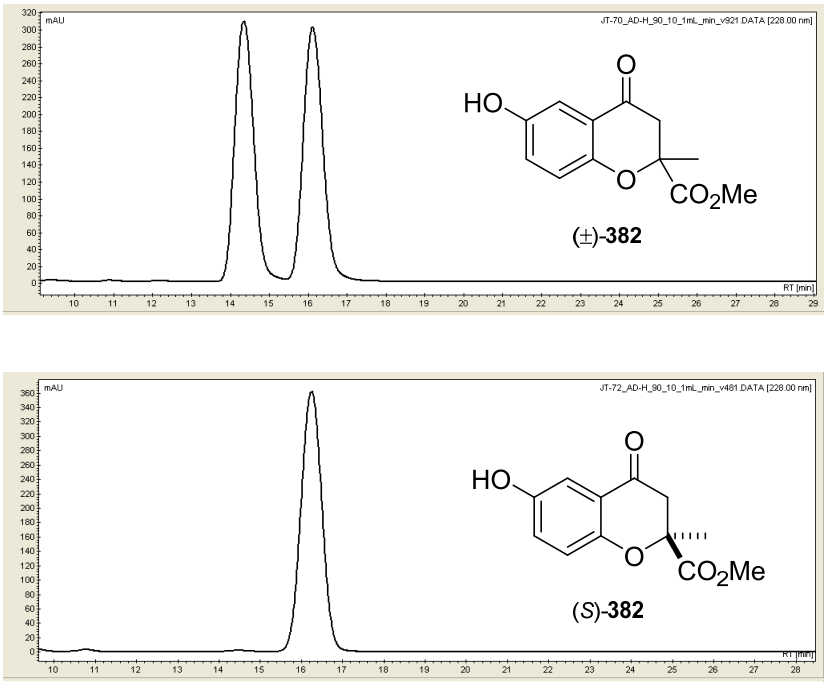
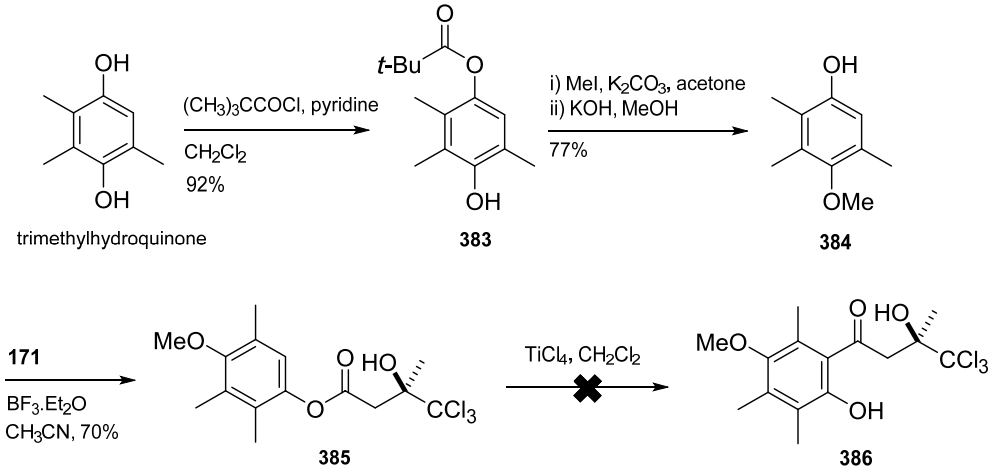


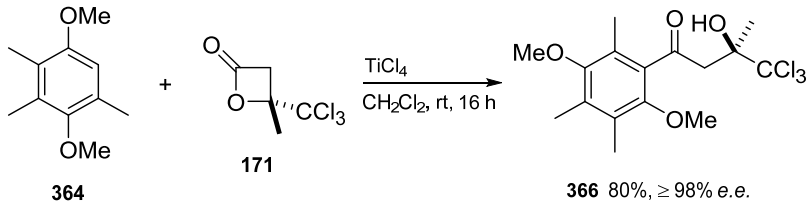
Figure 7. Top: HPLC trace of (±)-**382**. Bottom: HPLC trace of (*S*)-**382**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 90 : 10, 1 mL/min, 220 nm, (*R*) isomer 14.35 min, (*S*) isomer 16.12 min.

2.2 Synthesis of Aldehyde *35*

Having proved that we could synthesise chromane compounds in high enantiomeric excess using our Jocic reaction strategy, we turned our attention back to the synthesis of aldehyde **35**. Inspired by a report in the literature,[216] we hoped that the Fries rearrangement of **385** would give phenol **386** (Scheme 108). Unfortunately, the reaction of ester **385** failed to give any trace of phenol **386** even after heating at reflux temperature for three days. Thankfully, we found that using $TiCl_4$ in place of $AlCl_3$ in the ring-opening of lactone **171** gave the acylated compound **366** in good yield after optimisation of the reaction conditions (Scheme 109).



Scheme 108. Attempted synthesis of monoprotected phenol **386**.



Scheme 109. Successful ring opening reaction of lactone **171**.

The reaction failed or was very low yielding when fewer than 10 equivalents of the arene **364** were used, although a large proportion (~ 80%) could be recovered and reused. It was notable that the reaction was also low yielding when $TiCl_4$ was used as

a 1M solution in CH_2Cl_2, or when the neat $TiCl_4$ was more than a month old. Despite the large excess of **364**, the reaction is easily monitored using ^1H NMR spectroscopy by the change in chemical shift of the alkyl methyl group (highlighted, Figure 8). Compound **366** was then subjected to the same sequence of reactions previously developed, to yield 4-oxochromane ester **387** (Scheme 110). The racemate of ester **387** was prepared in the same way for HPLC analysis (Scheme 111). Figures 9 and 10 show that a high enantiomeric excess was maintained throughout the synthesis.

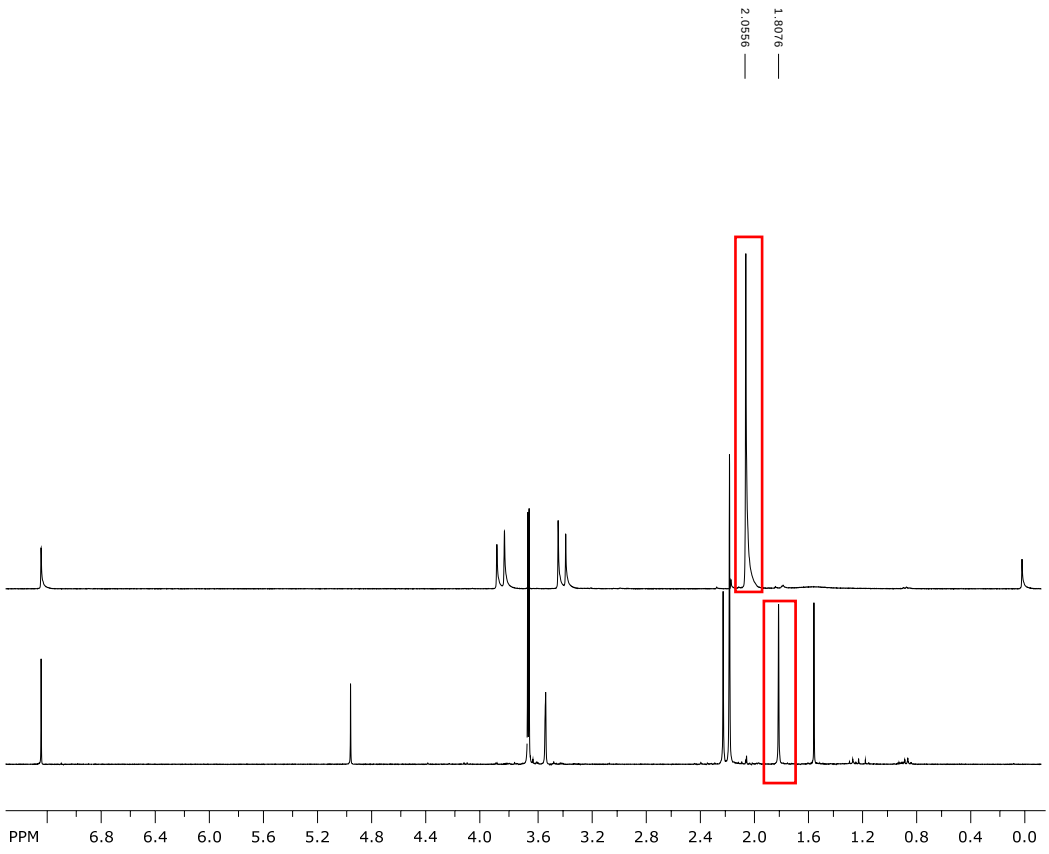
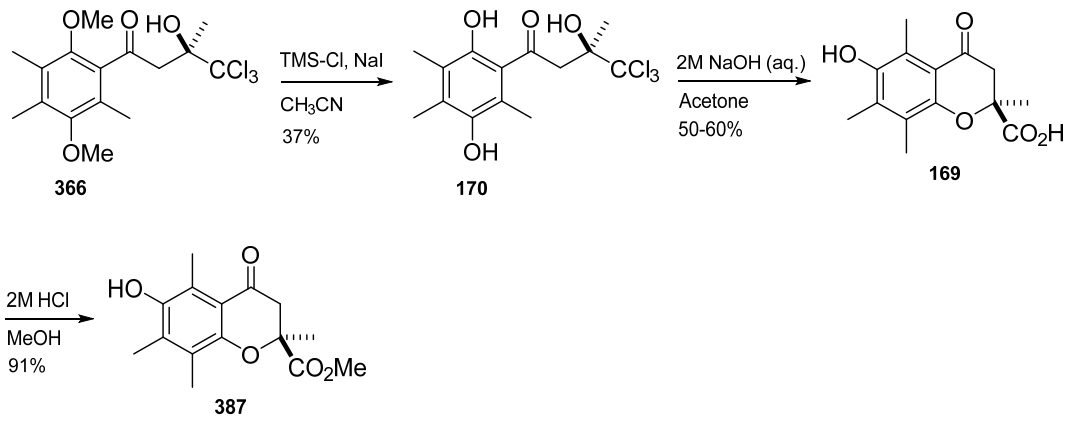
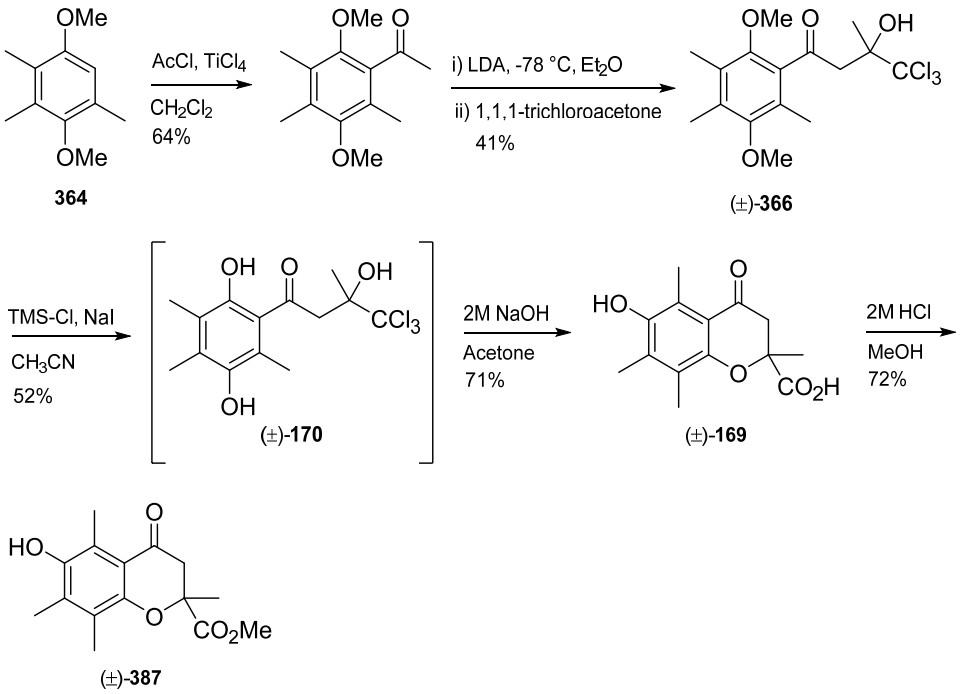


Figure 8. Top ^1H NMR spectrum: (*R*)-lactone **171**. Bottom ^1H NMR spectrum: compound **366**.



Scheme 110. Synthesis of ester **387**.



Scheme 111. Synthesis of racemate (±)-**387**.

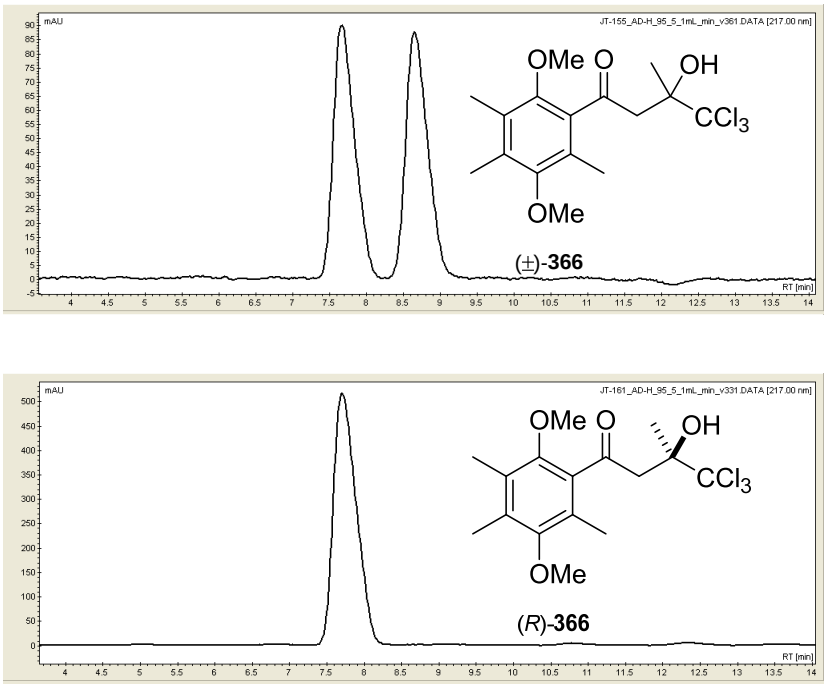


Figure 9. Top: HPLC trace of (±)-**366**. Bottom: HPLC trace of (*R*)-**366** Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 95 : 5, 1 mL/min, 214 nm, (*R*) isomer 7.67 min, (*S*) isomer 8.65 min.

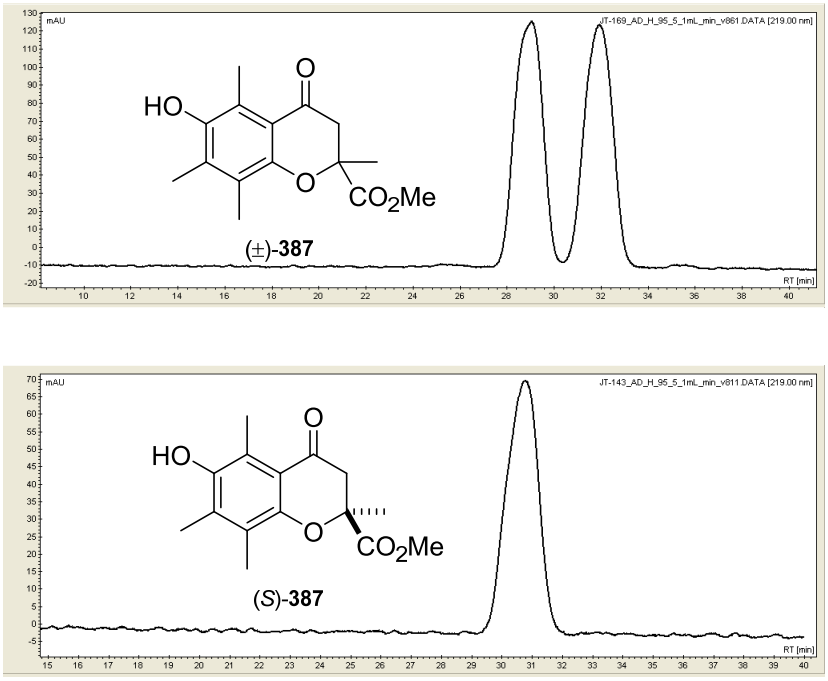
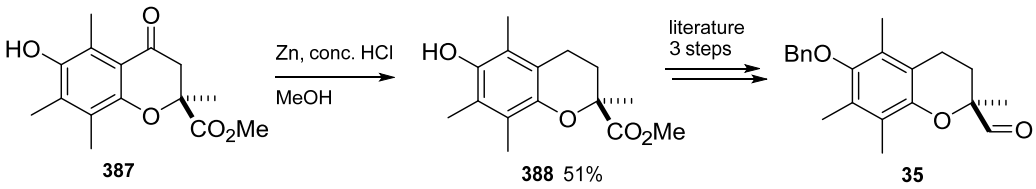


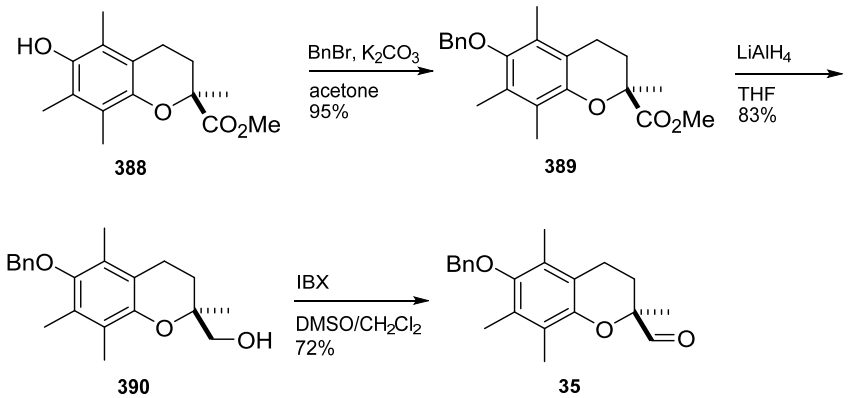
Figure 10. Top: HPLC trace of (±)-**387**. Bottom: HPLC trace of (*S*)-**387**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 95 : 5, 1 mL/min, 221 nm, (*S*) isomer 29.05 min, (*R*) isomer 31.92 min.

Despite the low yielding demethylation of the trichlorocarbinol **366**, multigram quantities of ester **387** could still be obtained through this route so we decided to continue the synthesis of aldehyde **35**. The synthesis of primary alcohol **390** had been reported from ester **388**,[140] and the oxidation of alcohol **390** was a known reaction[201, 394, 401](Schemes 112 and 113).



Scheme 112. Planned synthesis of aldehyde **35**.

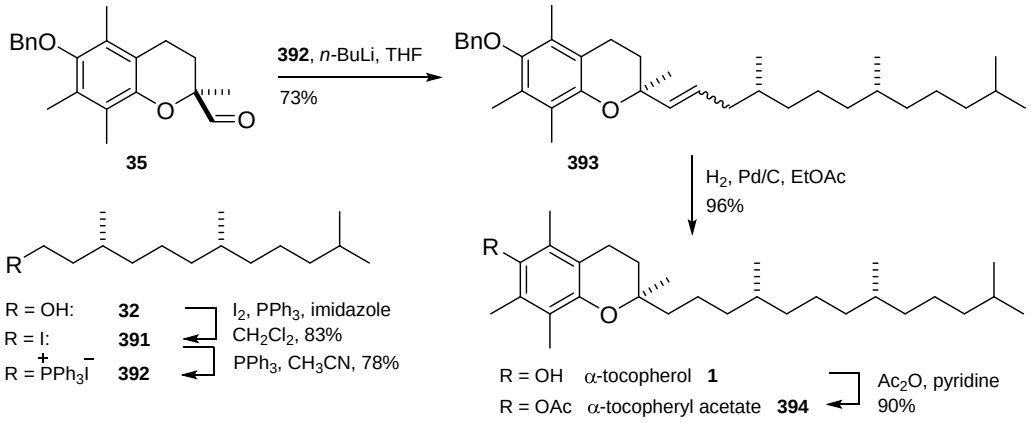
Therefore, all we had to do to get to known chemistry from our intermediate **387** was reduce the carbonyl group; this was achieved in 51% yield by using a Clemmensen reduction.[402] The remainder of the synthesis proceeded smoothly. The oxidising reagent 2-iodoxybenzoic acid (IBX)[403] was chosen over other common oxidation protocols (Swern, Parikh-Doering) as it was higher yielding. Additionally, the crude product was clean enough to be used in the next step without further purification.



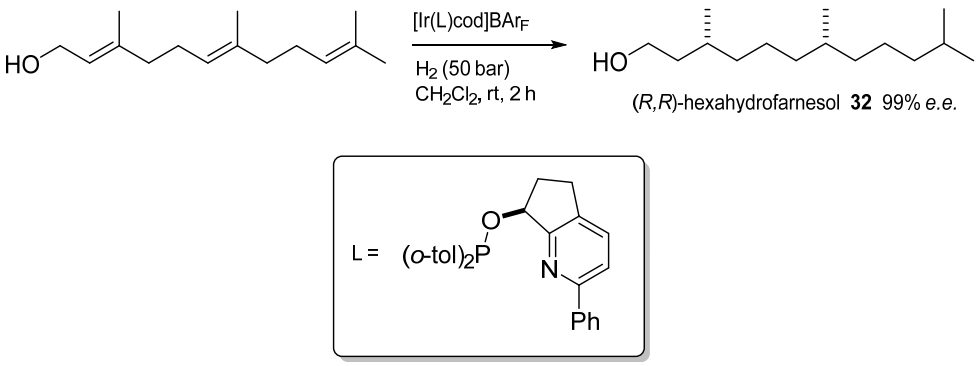
Scheme 113. Synthesis of aldehyde **35**.

2.3 Completion of the α-Tocopherol Synthesis

With aldehyde **35** in hand, the final steps in the synthesis consisted of the Wittig coupling of aldehyde **35** with the phosphonium salt **392**, followed by concurrent hydrogenation of the double bond and removal of the benzyl protecting group (Scheme 114). (*R*,*R*)-Hexahydrofarnesol **32** was provided by DSM Nutritional Products and it can be synthesised by the asymmetric hydrogenation of farnesol (Scheme 115).



Scheme 114. Completion of the synthesis of α-tocopherol **1**.



Scheme 115. Synthesis of (*R*,*R*)-hexahydrofarnesol. The supplied hexahydrofarnesol **32** was of the following stereochemical composition: (3*R*,7*R*) 93%, (3*S*,7*S*) 0%, (3*R*,7*S*) 5.8%, (3*S*, 7*R*) 0.75%. This corresponds to an *e.e.* (C-3) = 99% and *e.e.* (C-7) = 88%.

Both the ^{1}H and ^{13}C NMR spectra of our synthesised α-tocopherol **1** showed good correlation with an authentic sample (Figures 11 and 12). The phenol was protected as its acetate **394** to prevent ready oxidation of the compound.

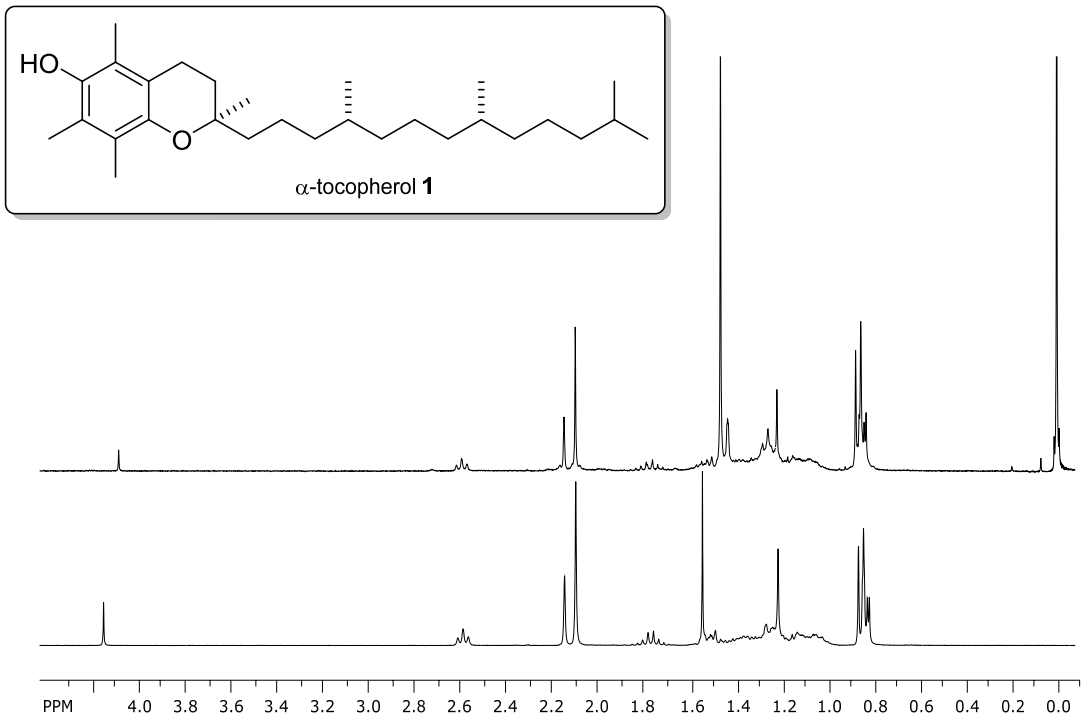


Figure 11. Top ^{1}H NMR spectrum: synthesised α-tocopherol **1**. Bottom ^{1}H NMR spectrum: authentic sample purchased from TCI (UK).

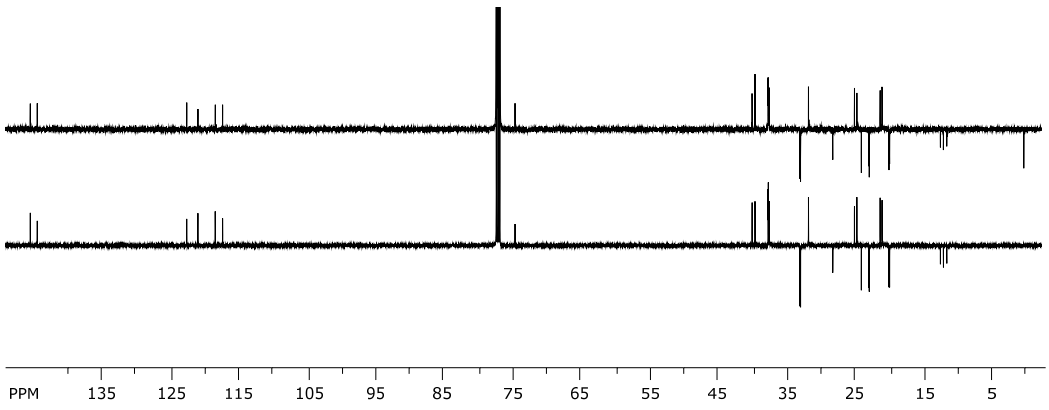
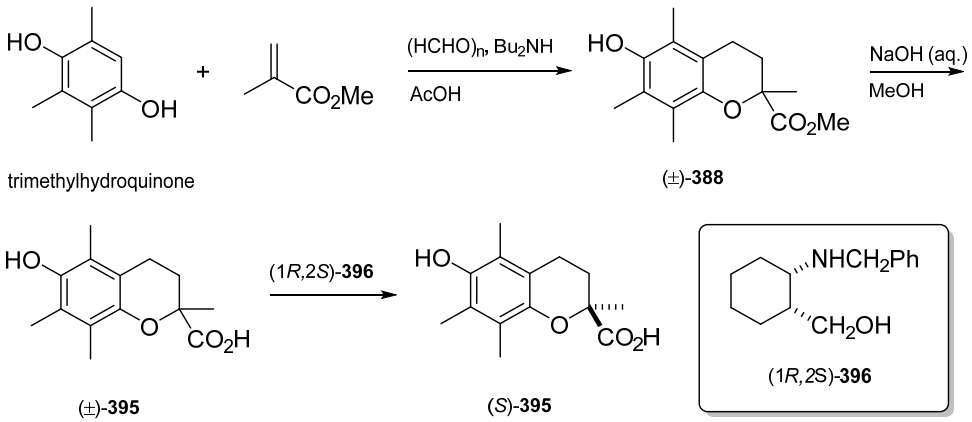


Figure 12. Top ^{13}C spectrum: Synthesised α-tocopherol **1**. Bottom ^{13}C spectrum: authentic sample purchased from TCI (UK).

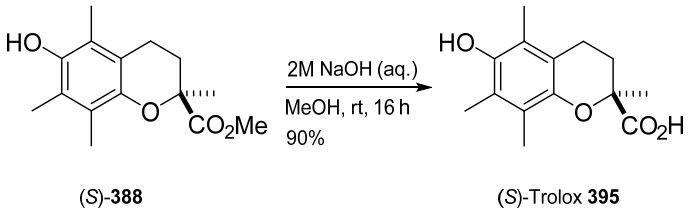
2.4 Trolox

Trolox, **395**, is a water-soluble vitamin E analogue which is known to prevent cell death by apoptosis.[404-407] This compound is commonly synthesised in racemic form *via* hydrolysis of the ester (±)-**388**, which in turn can be synthesised using a hetero-Diels-Alder reaction (Scheme 116).[408, 409] This carboxylic acid (±)-**395** can then be resolved using an amine base such as (1*R*,2*S*)-*cis*-2-(benzylamino)cyclohexylmethanol **396**.

We synthesised (*S*)-Trolox **395** by the hydrolysis of the previously synthesised ester (*S*)-**388** (Scheme 117).



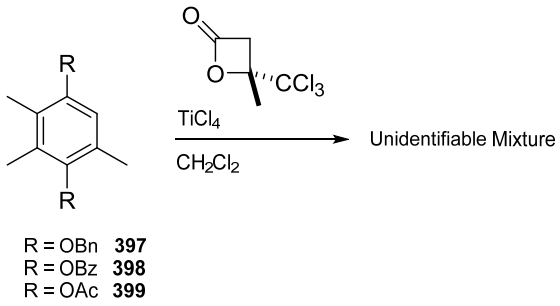
Scheme 116. Industrial synthesis of (*S*)-Trolox **395**.



Scheme 117. Synthesis of (*S*)-Trolox **395** by the hydrolysis of methyl ester (*S*)-**388**.

2.5 Revised Preparation of Methyl Ester 387

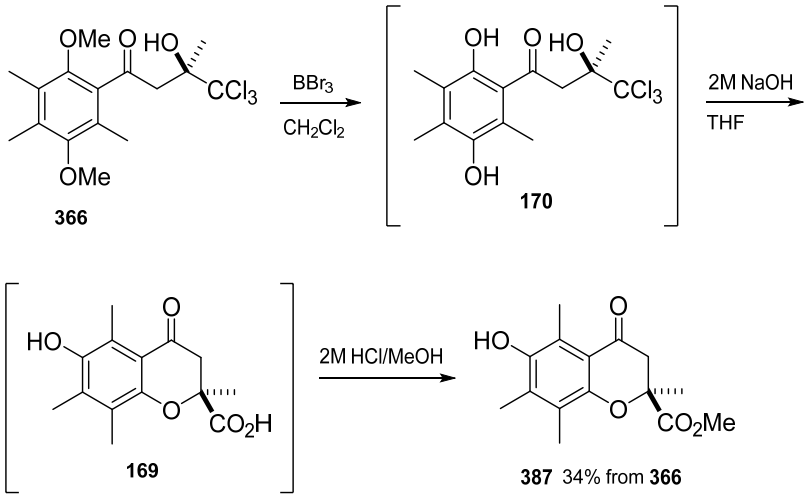
Having completed the synthesis of α-tocopherol **1**, we felt that the demethylation step in particular left a lot to be desired in terms of yield and ease of purification. Alternative protecting groups which would potentially be easier to remove (benzyl, benzoyl and acetyl) failed to survive the strongly acidic conditions of the Friedel-Crafts ring opening (Scheme 118).



Scheme 118. Attempted use of alternative phenol protecting groups.

Any methyl ether deprotection methods that required alkaline conditions, for example sodium thioethoxide in DMF,[410-412] were not considered due to the base-sensitive nature of the trichlorocarbinol group. In addition, due to the observed instability of the hydroquinone **170**, we sought a procedure where we could carry out the key Jocic reaction without isolation of this unstable intermediate.

In our original synthesis proposal we focused on milder demethylation methods because we were concerned about the stability of the trichlorocarbinol moiety; however, since the group survived the reaction with $TiCl_4$, it was shown to be more stable to Lewis acids than we imagined. BBr_3 is an extremely Lewis acidic reagent commonly used to remove methyl ethers,[413, 414] but one which was initially rejected by us due to its highly reactive nature. However, in light of the results obtained, we decided to test this reagent in the demethylation reaction of **366** (Scheme 119).



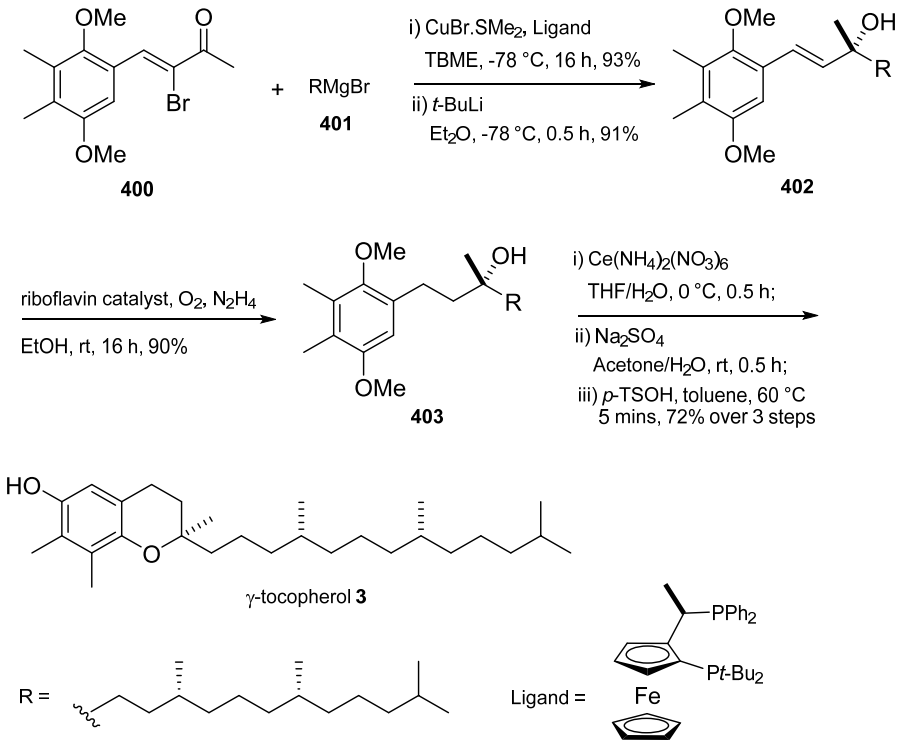
Scheme 119. Demethylation of aryl methyl ethers using BBr_3.

Pleasingly, treatment of **366** with BBr_3 gave complete conversion into **170**. In order to minimise exposure of hydroquinone **170** to air, the reaction was quenched under nitrogen and the CH_2Cl_2 solvent was removed under a flow of nitrogen. Redissolving this crude mixture in THF and adjusting the pH to 13-14 triggered the desired Jocic reaction. The carboxylic acid **169** was then directly esterified as a crude mixture to yield the methyl ester **387**, in a yield of 34% from **366**. This improved procedure provided the ester **387** in an approximately two-fold better yield than the previous synthesis, with the total reaction time reduced from five days to three days.

2.6 Synthesis of γ-Tocopherol

2.6.1 Previous Literature Syntheses

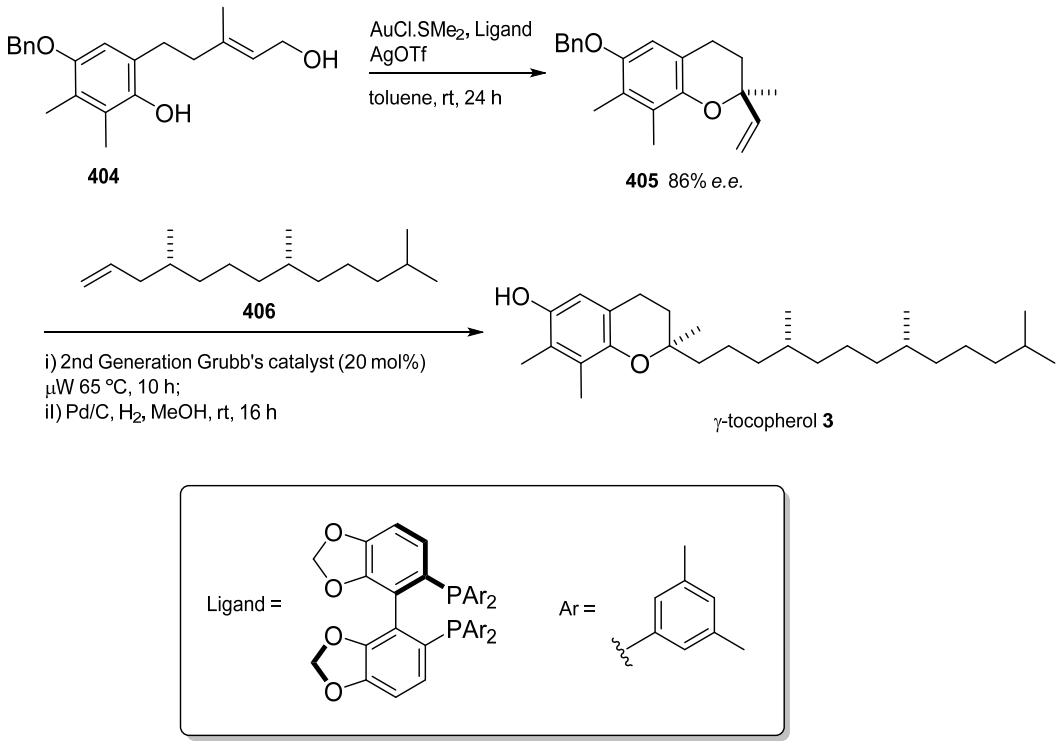
There are considerably fewer reports on the synthesis of γ-tocopherol compared to α-tocopherol, probably due to the higher biological activity of the α-form. The first asymmetric synthesis of γ-tocopherol was reported by Minnaard *et al*. (Scheme 120).[415]



Scheme 120. Total synthesis of γ-tocopherol.

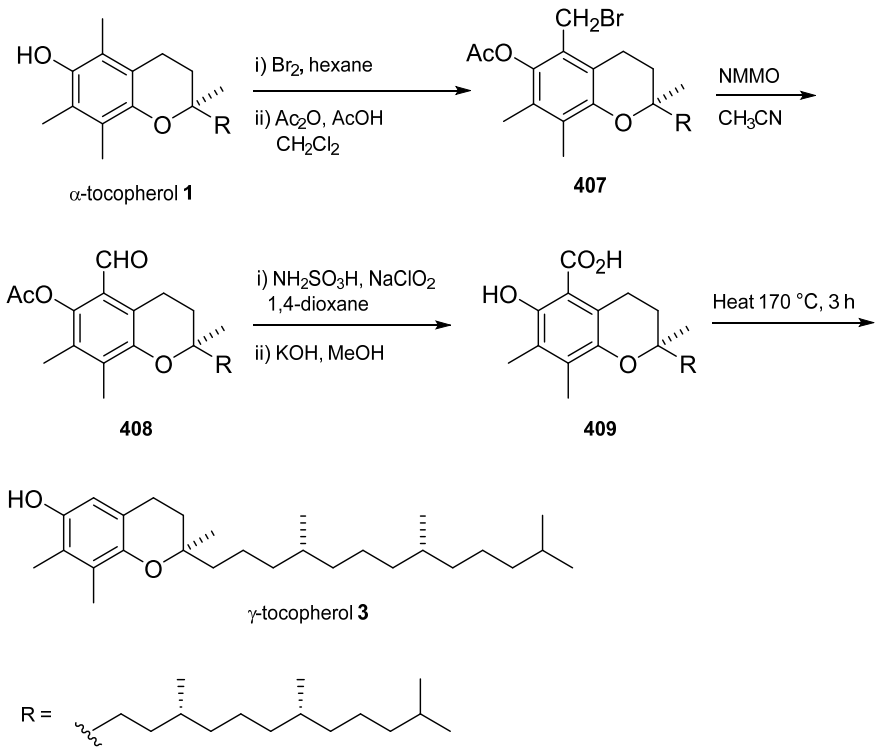
The key step was the asymmetric 1,2-addition of the Grignard reagent **401** to acetophenone **400**, using a chiral ferrocenyl ligand.[416, 417] Of the nine different ligands screened, the highest *d.e.* attained for the 1,2-addition was 73%. The Grignard reagent **401** was derived from natural phytol. Attempted hydrogenation of the allylic alcohol **402** using conventional metal catalysts (Pd/C, Pt/C, PtO_2) resulted in hydrogenolysis of the alcohol, hence the use of flavin catalysis.[418, 419] The remainder of the synthesis from compound **403** was carried out according to the synthesis of α-tocopherol by Cohen *et al.*[171]

In a synthesis by Reuping *et al.*, a gold-catalysed allylic substitution was used to produce vinyl chromane **405** with 86% *e.e.* (Scheme 121).[420] A cross-metathesis reaction with alkene **406**, obtained from the asymmetric hydrogenation of phytol by the method of Pfaltz,[164] yielded γ-tocopherol **3** after hydrogenation.



Scheme 121. Synthesis of γ-tocopherol by Reuping *et al.*

γ-Tocopherol is arguably most easily synthesised from commercially available α-tocopherol. Salvadori *et al.* synthesised γ-tocopherol by the aryl demethylation of α-tocopherol (Scheme 122).[421] This builds on previous work reported by Rosenau and Habicher,[422] who accomplished the decarboxylation of carboxylic acid **409** by photo-irradiation.

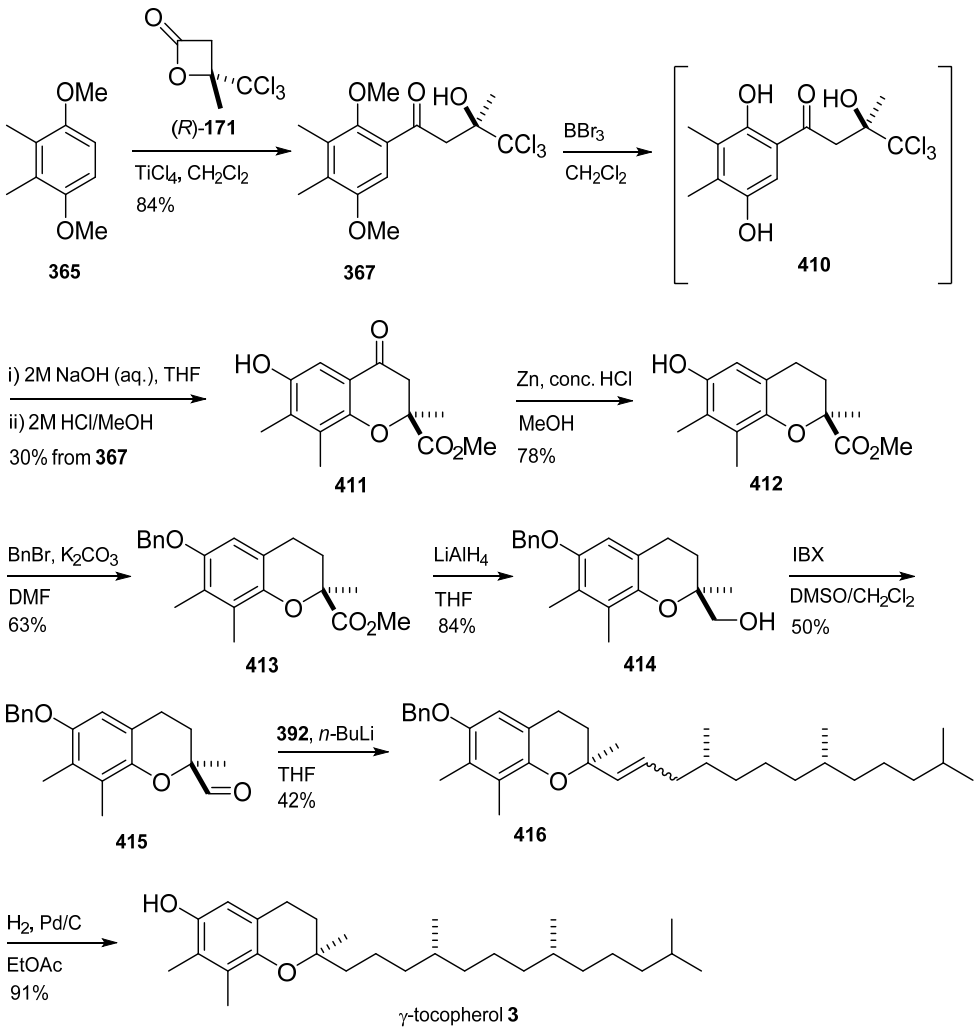


Scheme 122. Synthesis of γ-tocopherol by the demethylation of α-tocopherol.

2.6.2 Our Total Synthesis

Examples in the literature seemed scarce, and previous attempts at the asymmetric synthesis of γ-tocopherol had resulted in unsatisfactory enantiomeric excess at the C-2 centre. Therefore, we decided to synthesise γ-tocopherol **3** using our protocol (Scheme 123).

The synthesis started from 2,3-dimethyl-1,4-dimethoxybenzene **365**, which was synthesised using the same literature procedure as for **364** (see scheme 95). The rest of the synthesis proceeded using identical conditions to those used in the synthesis of α-tocopherol, with the exception that our demethylation/Jocic reaction procedure was used to give the ester **411** in comparable yield.



Scheme 123. Synthesis of γ-tocopherol.

The enantiomeric excess of ester **411** was measured to be ≥ 98% by chiral HPLC (Figures 13 and 14). This synthesis represents an improvement on previous reports in the literature where enantiomeric purity at the C-2 centre was unattainable. In addition, this work represents the first synthesis of γ-tocopherol by the popular Wittig coupling route on which the majority of asymmetric vitamin E syntheses are based.

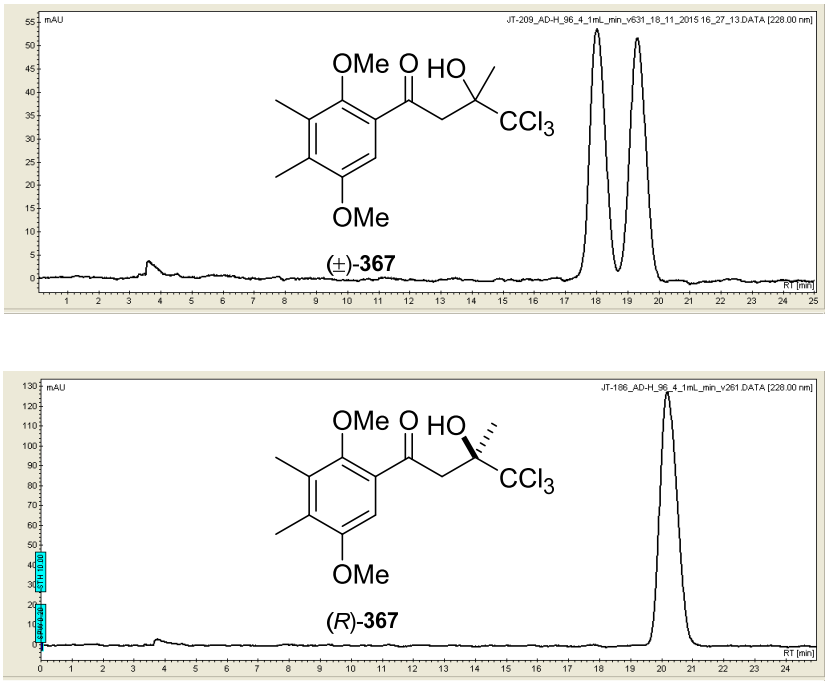


Figure 13. Top: HPLC trace of (±)-**367**. Bottom: HPLC trace of (*R*)-**367**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 4 : 96, 1 mL/min, 227 nm, (*S*) isomer 18.55 min, (*R*) isomer 19.88 min.

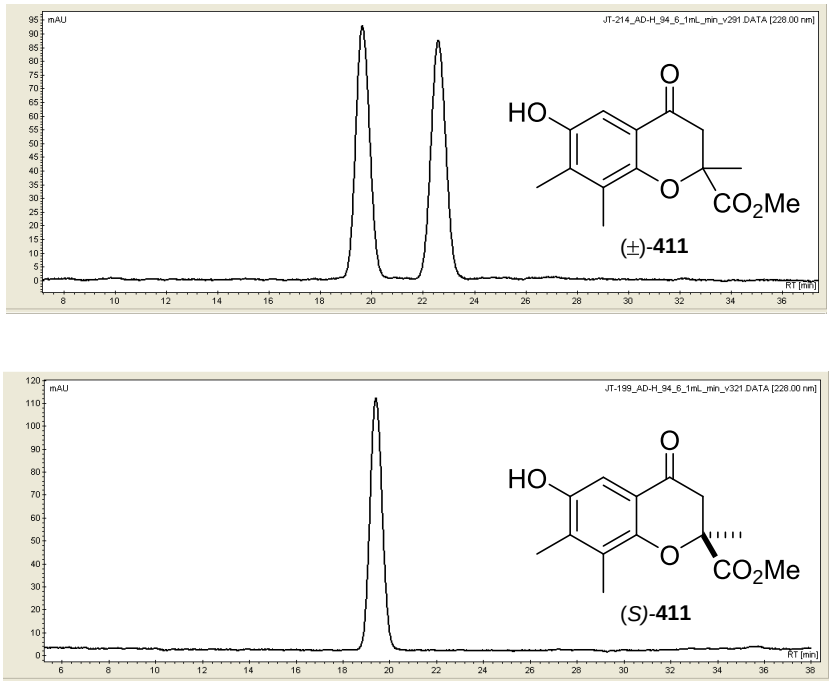


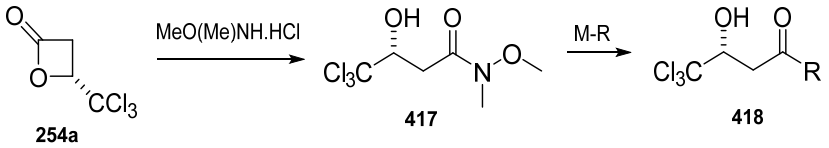
Figure 14. Top: HPLC trace of (±)-**411**. Bottom: HPLC trace of (*S*)-**411**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 6 : 94, 1 mL/min, 231 nm, (*S*) isomer 19.64 min, (*R*) isomer 22.59 min.

2.7 Other Tertiary Trichlorocarbinol Substrates

2.7.1 Reactions with Carbon Nucleophiles

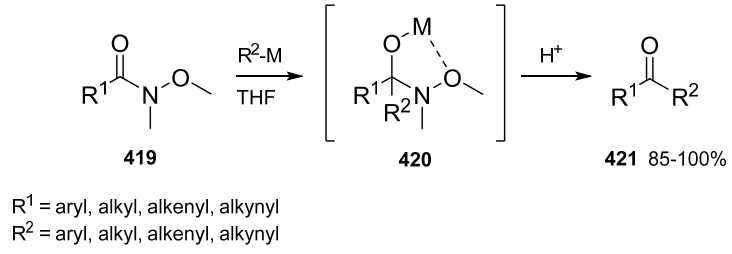
Given the success of the previous work, we were interested in potentially expanding the methodology to include nitrogen and sulfur-based nucleophiles, as well as altering the position of the intramolecular nucleophile in order to generate either 5- or 6-membered rings.

We anticipated that the lactone **171** would be susceptible to ring-opening by a variety of nucleophiles, and in addition it is a source of tertiary trichlorocarbinols which are hard to synthesise in high enantiomeric excess by other means. Using carbon-based nucleophiles as the starting point, it has been shown that using *N*-methoxy-*N*-methyl amide or morpholine amide derivatives prevents over-addition if lactones such as **254a** are directly reacted with organometallic reagents (Scheme 124).[355]



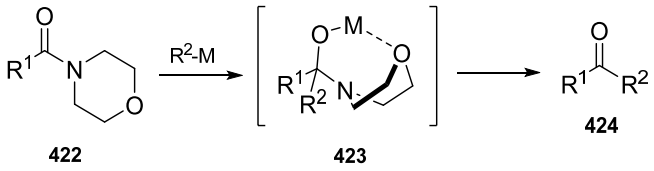
Scheme 124. Preparation of β-hydroxy(trichloromethyl) ketones. R = alkyl, aryl, allyl, vinyl.

N-Methoxy-*N*-methyl amides (Weinreb amides) are well known to afford a variety of ketones cleanly and in good yield on reaction with organolithium and Grignard reagents (Scheme 125).[423]



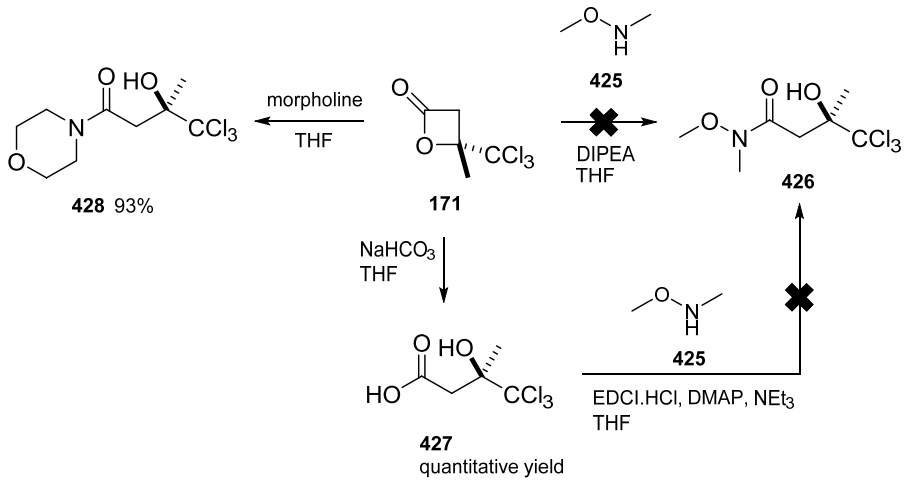
Scheme 125. Synthesis of ketones using Weinreb amides.

Little or no double addition is observed even with excess organometallic reagent. This is possibly due to metal chelation to the methoxy group which ensures that collapse of the tetrahedral intermediate **420** only occurs on work up, with simultaneous quenching of the excess organometallic species. Morpholine amides work by a similar mechanism (Scheme 126).[424]



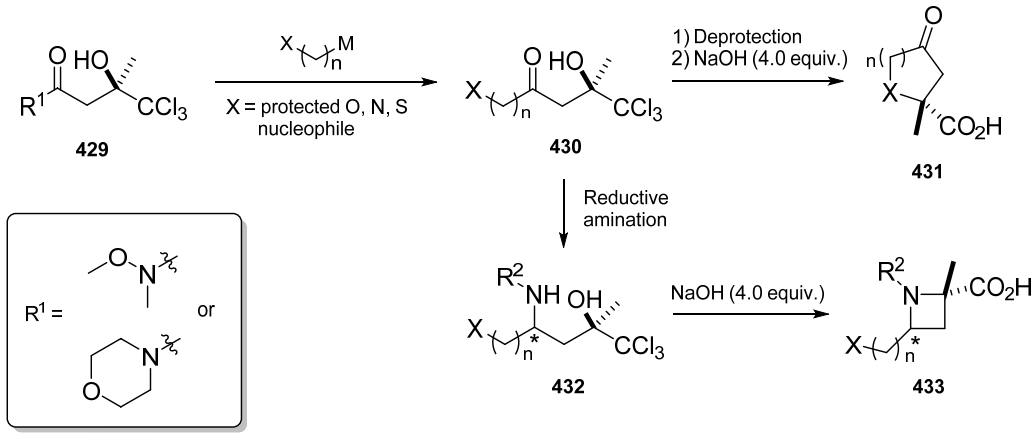
Scheme 126. Acylation of organometallic compounds using morpholine amide.

Ring opening of lactone **171** with *N*,*O*-dimethylhydroxylamine **425** was expected to give the amide **426** (Scheme 127), which could then undergo coupling with organometallic reagents. Our initial plan was that the organometallic species would contain a protected nucleophilic group, which would be unmasked to take part in an intramolecular Jocic reaction. The desired ketone product could also potentially undergo a reductive amination,[425, 426] followed by an intramolecular Jocic reaction, to yield substituted azetidines (**433**) in diastereoselective fashion (Scheme 128).



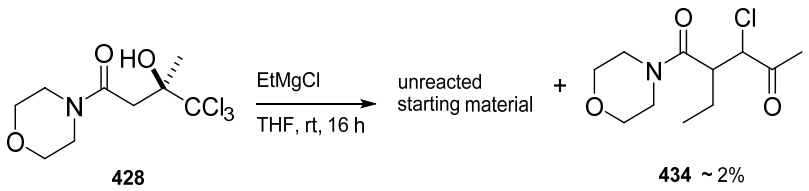
Scheme 127. Synthesis of morpholine amide **428**. DIPEA = diisopropylethylamine, DMAP = *p*-dimethylaminopyridine.

Unfortunately, attempts to synthesise the Weinreb amide **426** failed, either by a reported direct ring opening of the lactone **171** or by coupling with carboxylic acid **427** using an acid activating reagent. However, the lactone underwent ring opening readily with morpholine to give the amide **428**. Microwave conditions were chosen since the required reaction time was greatly reduced compared to conventional heating.



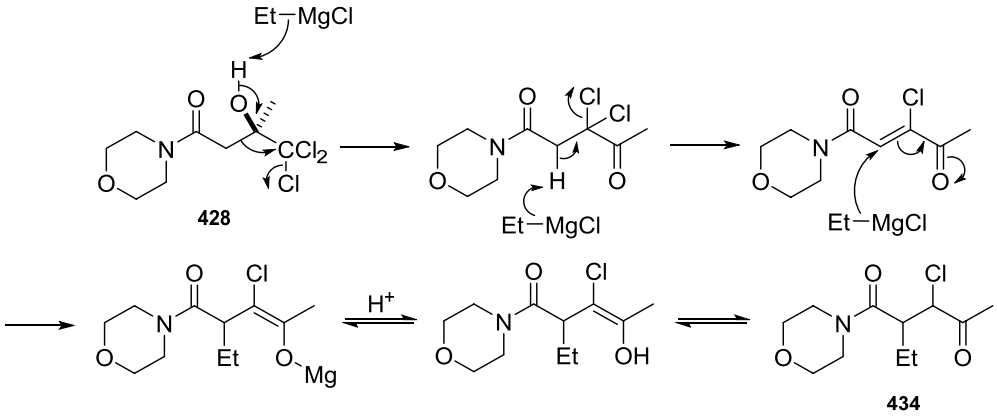
Scheme 128. Proposed synthesis of cyclic structures using an intramolecular Jocic reaction.

With the morpholine amide **428** in hand, we first sought to test the reaction using EtMgCl as a simple Grignard reagent. Unfortunately, the expected ketone was not observed under any of the conditions tested. Using two equivalents of EtMgCl in THF at room temperature overnight yielded largely unreacted starting material, with a small amount of an unknown side product (Scheme 129). This was eventually identified by ^{1}H and ^{13}C NMR spectroscopy as compound **434** (Figure 15) and two mechanisms for its formation are proposed (Schemes 130 and 131). In addition, the crude ^{1}H NMR spectrum showed the presence of unsaturated compounds, although these could not be identified.

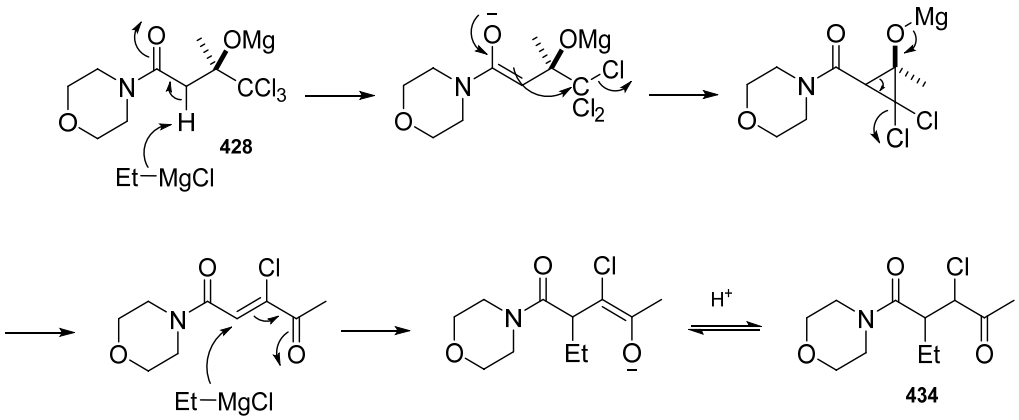


Scheme 129. Unexpected formation of compound **434**.

The alkyl migration proposed in scheme 130 bears similarity to other well-known rearrangements which involve migration to electron deficient nitrogen, in particular the Lossen,[427] Curtius,[428] Schmidt,[429] Beckmann[430] and Tiffenau-Demjanov[431] rearrangements. Migrations of this type have not been reported for trichlorocarbinol compounds. The second mechanism (Scheme 131) requires the formation of a dichlorocyclopropane.[432, 433]



Scheme 130. Mechanism for the formation of compound **434** involving an alkyl migration.



Scheme 131. Mechanism for the formation of compound **434** *via* a cyclopropane rearrangement.

The EtMgCl is acting as both a base and a nucleophile in both mechanisms. Compound **434** was isolated as a single diastereoisomer, with the other diastereoisomer being inseparable from the unreacted starting material. The crude mixture showed an approximate 2.5:1 ratio of these diastereoisomers, with the major isomer being the one isolated (Figure 15).

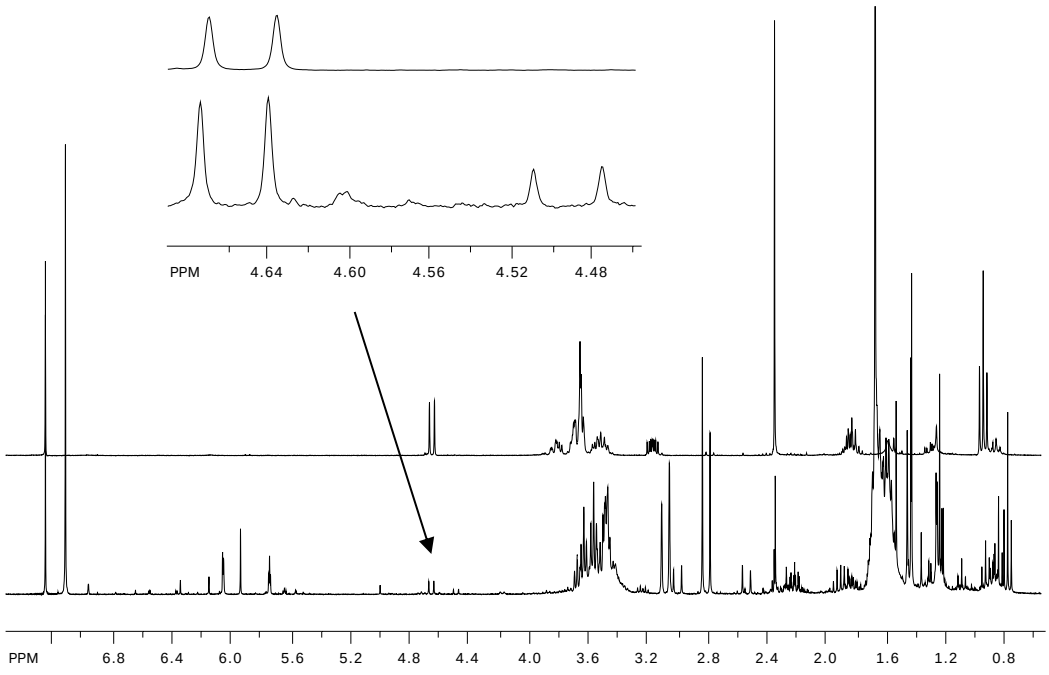
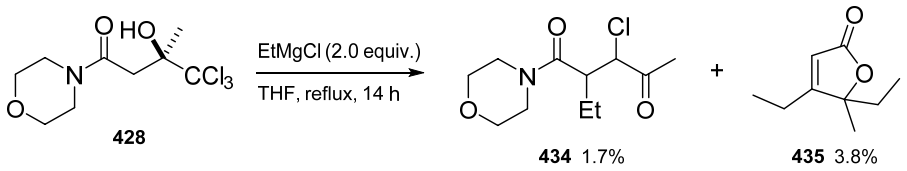


Figure 15. Top ^{1}H NMR spectrum: isolated single diastereoisomer of compound **434**. Bottom ^{1}H NMR spectrum: crude reaction mixture. Inset: C*H*Cl doublets.

In an attempt to increase the yield of **434** the reaction was carried out under elevated temperatures, from 40 °C to reflux (Scheme 132). At reflux temperature, lactone **435** (Figure 16) was formed in addition to amide **434**. Its formation can be rationalised by either of the mechanisms shown in schemes 133 and 134.



Scheme 132. Unexpected formation of lactone **435**.

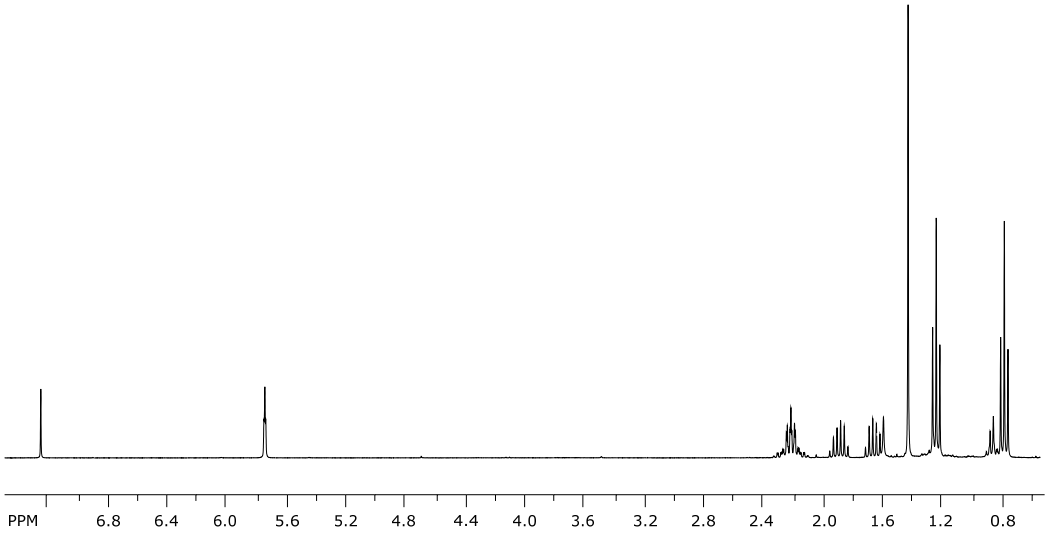
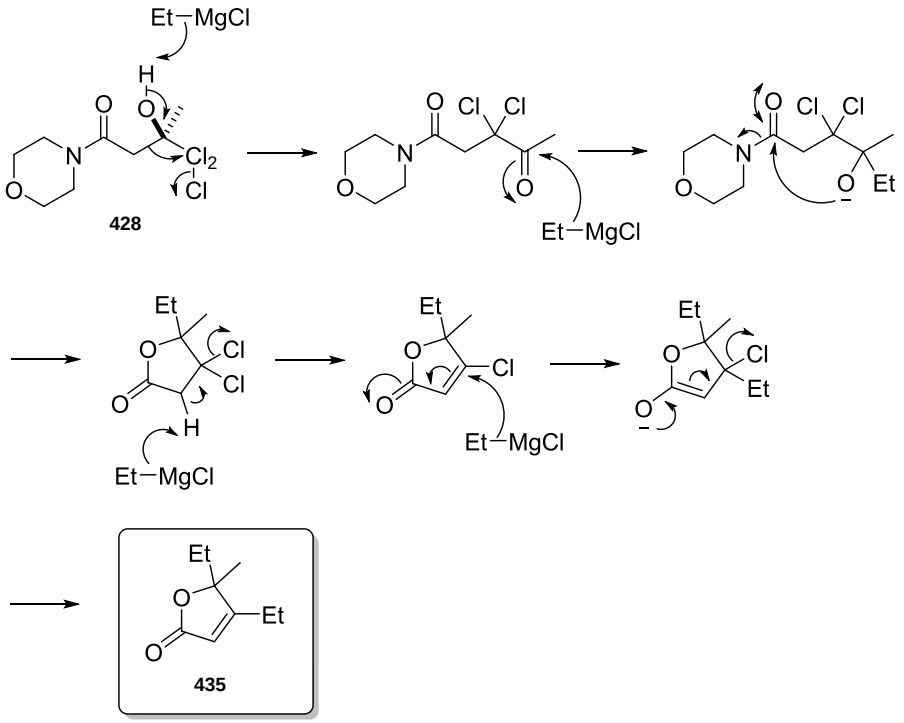
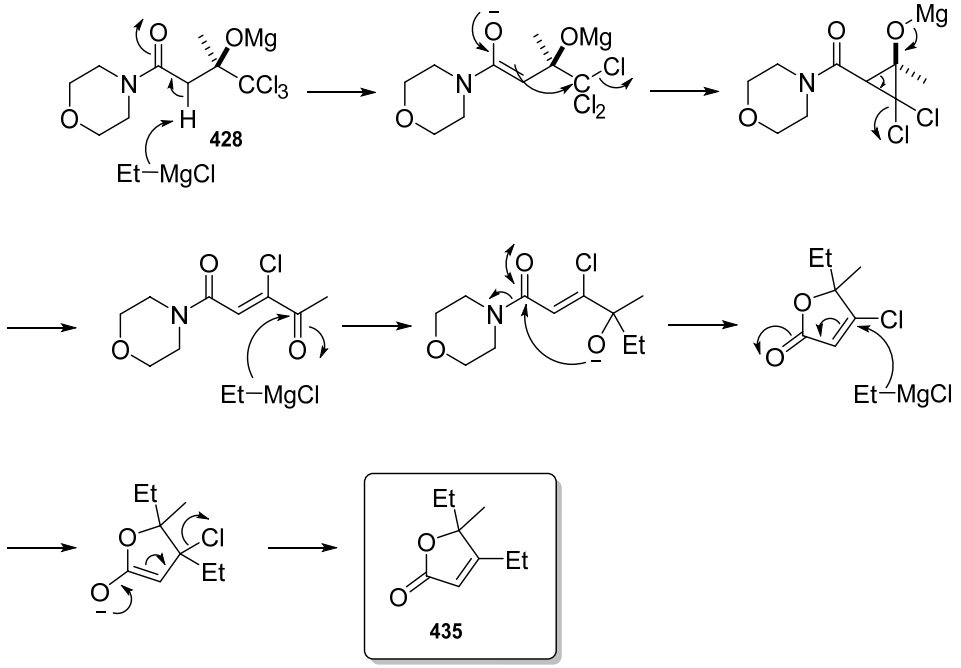


Figure 16. [1]H NMR spectrum of isolated lactone **435**.

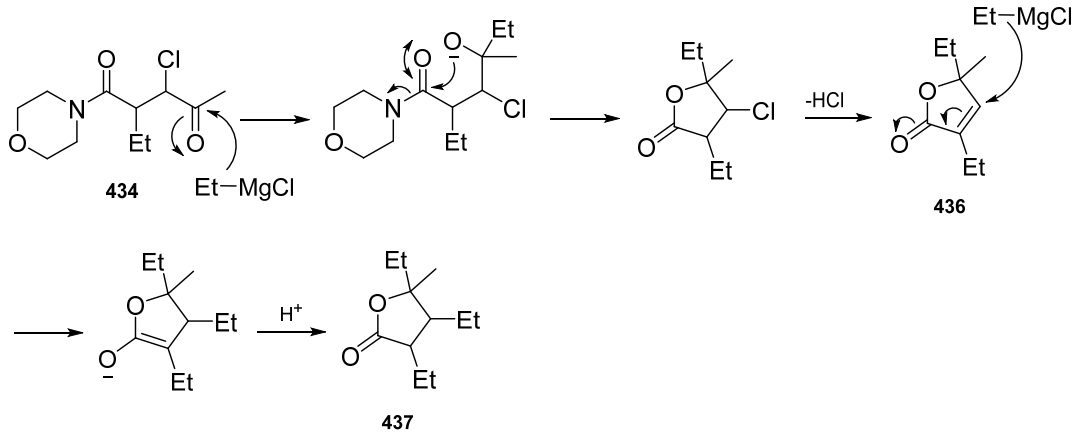


Scheme 133. Potential mechanism for the formation of lactone **435**.



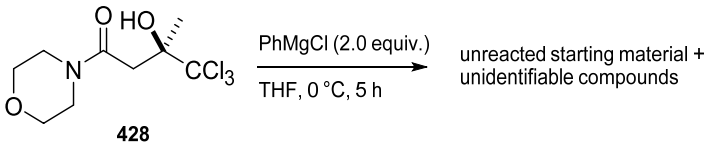
Scheme 134. Potential mechanism for the formation of lactone **435**.

The two mechanisms proposed for the formation of lactone **435** involve either an alkyl migration or a cyclopropane rearrangement. The γ-keto amide **434** cannot be an intermediate in the reaction mechanism as this would yield the lactones **436** or **437**. (Scheme 135).



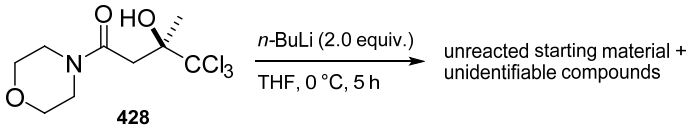
Scheme 135. Potential mechanisms for the formation of lactones which were not observed in the reaction mixture.

The reaction with PhMgCl yielded largely unreacted starting material with some unidentifiable side products (Scheme 136). None of the desired addition to the morpholine amide was observed.



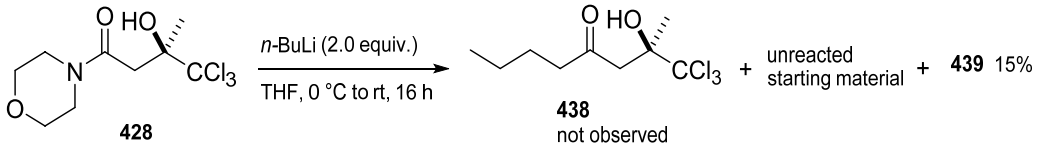
Scheme 136. Unsuccessful reaction with phenylmagnesium chloride.

Grignard reagents had appeared to be unsuitable, so organolithium reagents were explored instead. The reaction with *n*-butyllithium appeared to give none of the desired addition product (Scheme 137).



Scheme 137. Reaction of morpholine amide **428** with *n*-BuLi.

At 0 °C the crude reaction mixture was largely unreacted starting material. However, when the reaction was stirred at 23 °C for 16 hours more of the starting material was consumed. Unfortunately, it was not converted into the ketone **438** but mainly into a compound **439** which we were unable to identify (Scheme 138 and Figure 17).



Scheme 138. Reaction of morpholine amide **428** at elevated reaction temperature and time.

This compound was not a result of addition of the organolithium to the amide, since the broad peak between 3.95-3.32 ppm can be assigned to the protons on the morpholine ring. Peaks corresponding to vinyl protons were also present (5.13, 5.04

and 4.90 ppm), as well as incorporation of two butyl groups (triplet at 0.91 integrates to six protons).

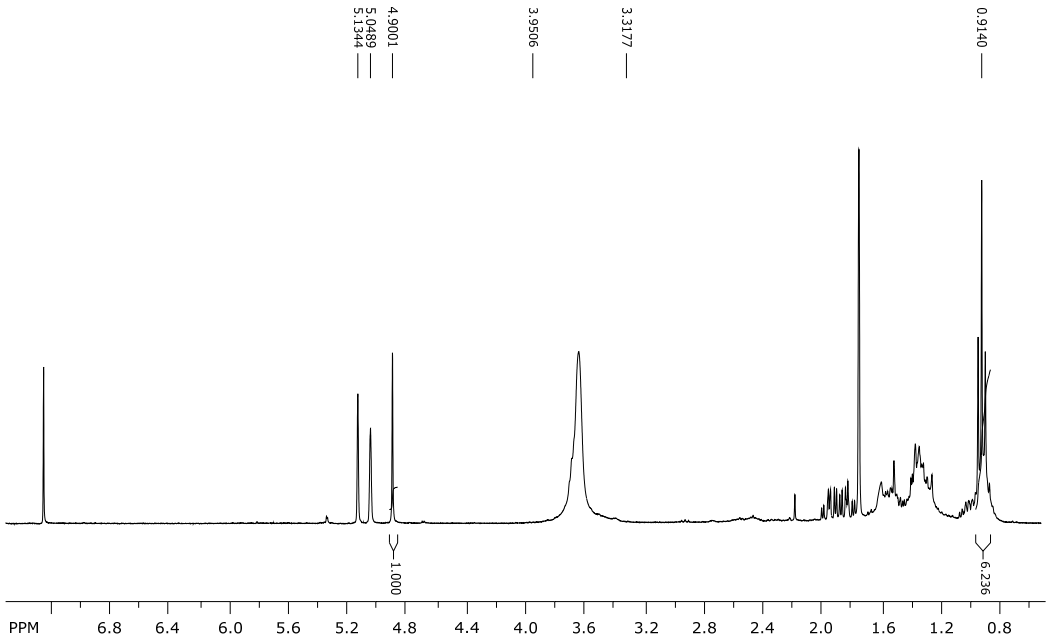
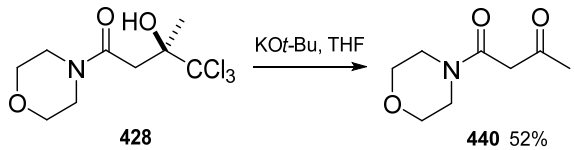


Figure 17. ^{1}H NMR of isolated side product **439**.

Even with the use of HSQC and HMBC correlation experiments we were not able to positively identify this compound.

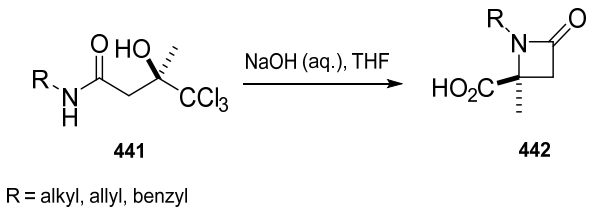
When KO*t*-Bu was used as a strong, non-nucleophilic base, the sole product obtained was 1-morpholinobutane-1,3-dione **440**, by elimination of $CHCl_3$ (Scheme 139). These results indicate that the EtMgCl potentially has some function as a Lewis acid assisting the chloride leaving in all of the mechanisms previously discussed.



Scheme 139. Elimination of $CHCl_3$ from amide **428**.

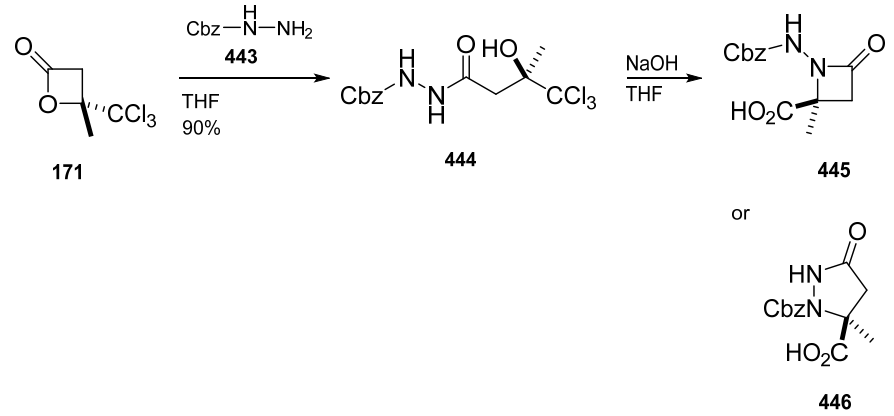
2.7.2 Reactions with Nitrogen Nucleophiles

Using organometallic reagents in the presence of the trichlorocarbinol functional group had proved troublesome. However, amides of the type **441** are readily synthesised in high yields. Ongoing work in the group had shown that amides such as **441** will ring close when treated with four equivalents of NaOH, to produce β-lactams with complete stereocontrol (Scheme 140).

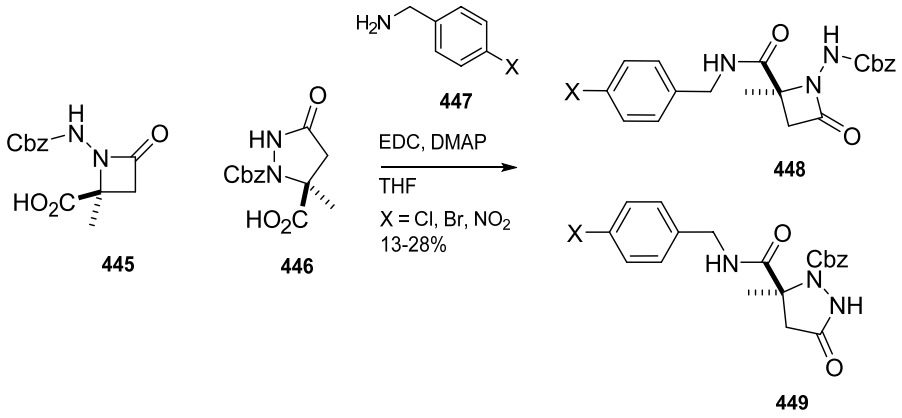


Scheme 140. Intramolecular Jocic reaction to produce β-lactams.

Hydrazine compounds offer a potentially interesting extension to this type of reaction, as there should now be two competing nucleophiles in the Jocic reaction. Benzyl hydrazinecarboxylate was the first compound studied and the corresponding amide, **444**, has the potential to form either a 4-membered ring (β-lactam) or a 5-membered ring (pyrazolidin-3-one). Amide **444** was prepared by the ring opening of lactone **171** with hydrazine **443**, and was subsequently subjected to the standard Jocic conditions to yield either β-lactam **445** or pyrazolidin-3-one **446** (Scheme 141). Given that the product was not crystalline and that it was not possible to determine which structure was formed based on NMR data alone, we planned to couple β-lactam **445** or pyrazolidin-3-one **446** with a benzylamine compound in the hope that the amide would be crystalline for X-ray crystallography analysis (Scheme 142).



Scheme 141. Proposed synthesis of cyclic structures using an intramolecular Jocic reaction.



Scheme 142. Amide synthesis.

Unfortunately, of the amide derivatives synthesised, suitable crystals could not be grown. Attempts to remove the Cbz group to give a potentially more crystalline compound resulted in degradation of the material. However, by comparing the infrared data to the literature we were able to make a tentative assignment (Figure 18).[434]

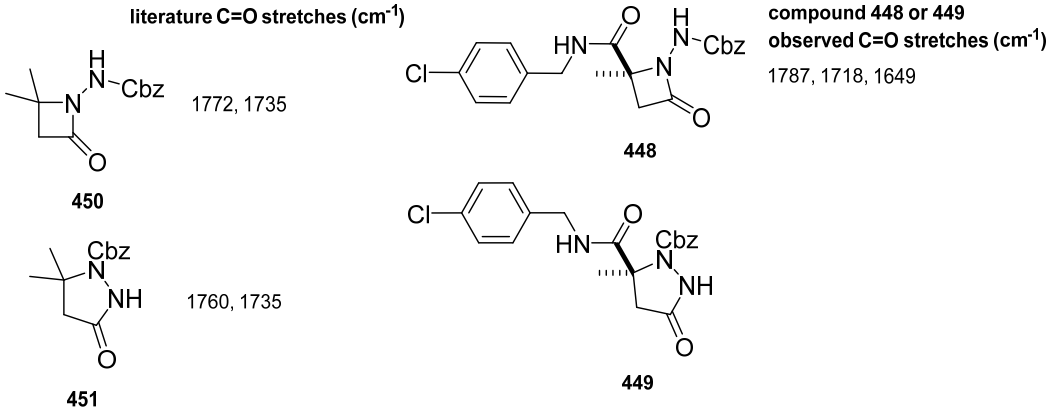
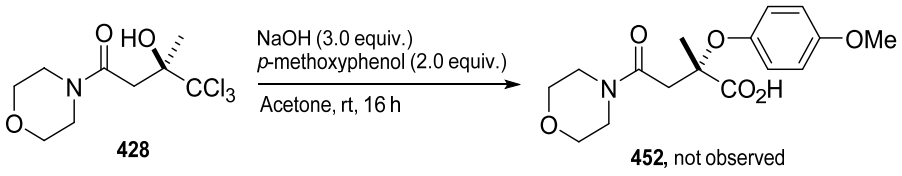


Figure 18. Comparison of IR data to the literature.

The higher frequency absorption in the known compounds **450** and **451** can be assigned to the β- and γ-lactam C=O stretches, respectively. Compound **448** or **449** showed a highest C=O stretch of 1787 cm^{-1}. β-Lactam **448** is therefore the most likely structure based on the data available to us, although this is not conclusive evidence.

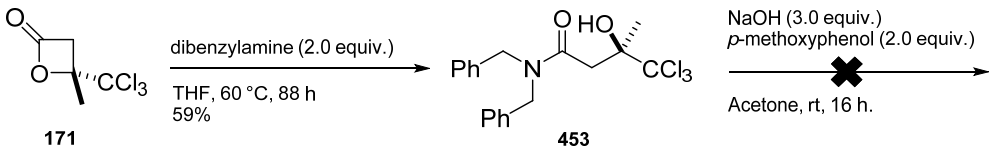
2.7.3 Reactions with Oxygen Nucleophiles

Treatment of amide **428** with NaOH and *p*-methoxyphenol was anticipated to yield the phenoxy-substituted acid **452** (Scheme 143), since there was precedent in the literature for phenoxide to act as a nucleophile in the Jocic reaction.[336, 435] Unfortunately, the reaction failed to give any identifiable products. Since the Bargellini reaction is almost exclusively the reaction of phenoxide nucleophiles with tertiary trichlorocarbinols (generated *in situ*), it is unclear as to why the reaction in scheme 143 should fail completely. The reason cannot be slower formation of the intermediate *gem*-dichloroepoxide since the rate of this step will be enhanced for tertiary trichlorocarbinols due to the Thorpe-Ingold effect.[436, 437]



Scheme 143. Attempted Jocic reaction with 4-methoxyphenol.

The amide **453** was also synthesised as a substrate for the same reaction, by ring opening of lactone **171** with dibenzylamine (Scheme 144).



Scheme 144. Attempted Jocic reaction using an alternative amide.

Dibenzyl amide **453** should be more stable to alkaline hydrolysis than the potentially labile morpholine amides. Unfortunately, the Jocic reaction with this amide also failed to yield any identifiable products.

2.8 Conclusions and Future Work

The asymmetric syntheses of both natural products α-tocopherol and γ-tocopherol were completed. The asymmetric synthesis of γ-tocopherol had previously only been achieved by a gold-catalysed allylic substitution or by an enantioselective 1,2-addition. Neither of these syntheses managed to achieve a high enantiomeric excess at the tertiary C-2 centre. In this sense, our work represents an improvement on the previously reported work since we were able to achieve ≥ 98% *e.e.* at the C-2 centre.

The key step in the synthesis was an intramolecular Jocic reaction which proceeded with complete inversion and retained the ≥ 98% enantiomeric excess of the trichlorolactone starting material. Difficulties during the synthesis included the Friedel-Crafts ring opening of a β-lactone with a sterically hindered dimethoxybenzene, and the demethylation of aryl methyl ethers. The Friedel-Crafts reaction was found to be mediated by $TiCl_4$ in high yield, whilst BBr_3 was eventually used to remove the methyl ethers. Despite the strongly Lewis acidic nature of both reagents, no degradation of our substrate was observed. Trichlorocarbinols are particularly stable to acidic conditions due to the electron withdrawing CCl_3 moiety. The later steps in the synthesis were known in the literature and proceeded smoothly.

The water-soluble vitamin E analogue (*S*)-Trolox could also be obtained by hydrolysis of one of the intermediate ester compounds. β-Tocopherol is also theoretically obtainable using the synthesis we developed, if 2,5-dimethyl-1,4-dimethoxybenzene is used as the arene starting material.

The reaction is a potentially useful general synthesis of tertiary chromanes which have been shown to be difficult to access in high enantiomeric excess by other methods. Aniline or thiphenol analogues should in theory yield 2-substituted tetrahydroquinolines and thiochromanes, respectively. Trichlorolactones with

different substitution patterns are known, and these would offer different substitution at the 2-position of the chromane ring.

In addition, attempts were made to expand the methodology to include inter- rather than intramolecular nucleophiles. The attempted addition of organometallic reagents to a morpholine amide containing the trichlorocarbinol group failed to give the expected ketone product, with the reaction instead yielding several unexpected compounds. Attempts to use *p*-methoxyphenol as a nucleophile in the Jocic reaction with this amide also failed to yield the expected α-disubstituted carboxylic acid, whereas the intramolecular version gave reasonable yields of cyclised product during the synthesis of the tocopherols **1** and **3**. Despite this lack of success, we felt that further studies using lactone **171** as a masked source of an enantiomerically enriched trichlorocarbinol were warranted as there were very few examples of this in the literature.

2.9 Experimental Section

All the reagents and solvents used were purchased from Sigma-Aldrich, Alfa-Aesar, TCI, Fluorochem or Acros Organics and were used as received unless stated otherwise. Solvents were dried over 3 Å or 4 Å molecular sieves where necessary.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVII-700 MHz, AVIII HD-500 MHz, AVIII HD-400 MHz, AVIII HD-300 MHz or AV-300 MHz Fourier transform spectrometer, at room temperature unless stated otherwise. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane. Solvents were used as an internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, $(CD_3)_2SO$ 2.50 ppm, D_2O 4.79 ppm; δ_C: $CDCl_3$ 77.1 ppm, CD_3OD 49.0 ppm, $(CD_3)_2SO$ 39.5 ppm). Coupling constants (*J*) are quoted in Hertz (Hz) and rounded to the nearest 0.5 Hz. Abbreviations used in the descriptions of spectra are as follows; s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded with proton decoupling and the spectra were assigned on the basis of COSY, PENDANT, HSQC and HMBC experiments.

Infrared spectra were recorded on a Bruker ALPHA platinum ATR spectrometer using OPUS software and are quoted in wavenumbers (cm^{-1}).

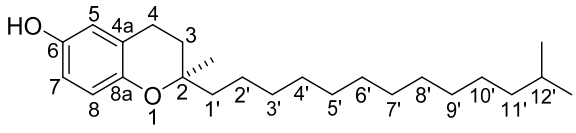
Optical rotations were recorded on an Optical Activity Ltd. AA-1000 millidegree auto-ranging polarimeter (using the sodium D line, 589 nm) and $[\alpha]_D$ values are given in units of 10^{-1}deg cm^2 g^{-1}. The samples were prepared using spectroscopic grade $CHCl_3$ or MeOH.

HPLC data were obtained on a Varian Prostar 335LC detector using a Chiralcel Daicel AD-H column (4.6 mm x 250 mm), with a solvent system of *n*-hexane:2-propanol.

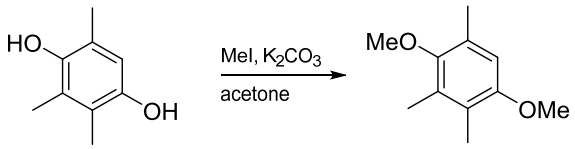
Melting points for solid crystalline products were determined using a Stuart Scientific SMP10 Digital Melting Point Apparatus, with a range given in °C and rounded to the nearest degree. The melting points are uncorrected.

Thin Layer Chromatography (TLC) was carried out using silica coated (0.25 mm) alumina plates, and the plates were visualised using UV light or staining by $KMnO_4$.

Tocopherol-derived compounds are numbered according the following IUPAC system:



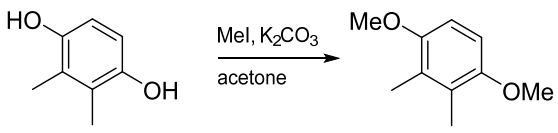
1,4-Dimethoxy-2,3,5-trimethylbenzene 364



364

The compound was prepared according to a method adapted from the literature.[397] To a solution of trimethylhydroquinone (10.0g, 64.7 mmol) in acetone (100 mL) was added K_2CO_3 (36.3g, 263 mmol) and MeI (16.4 mL, 263 mmol) under nitrogen, and the mixture was stirred for 48 hours at reflux temperature. The solvent was removed *in vacuo*, water was added and the compound was extracted with Et_2O. The combined organic layers were washed with water and dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was purified by column chromatography (95:5 petroleum ether/Et_2O) to give the product as a white solid (9.70 g, 82%). ν (cm^{-1}); 2936 (C-H stretch), 1120 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (1H, s, Ph-H), 3.80 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 2.31 (1H, s, Ar-CH_3), 2.23 (1H, s, Ar-CH_3), 2.15 (1H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6 (*C*OCH_3), 150.7 (*C*OCH_3), 130.7 (Ph-C), 127.9 (Ph-C), 123.6 (Ph-C), 110.4 (Ph-CH), 60.2 (OCH_3), 55.8 (OCH_3), 16.3 (CH_3), 12.7 (CH_3), 11.9 (CH_3); LRMS (ESI) *m*/*z*: calcd. for $C_{11}H_{16}NaO_2$ $[M+Na]^+$ 203.1, found 203.2; m.p = 35-36 °C. Data are consistent with that previously reported.[397]

1,4-Dimethoxy-2,3-dimethylbenzene 365

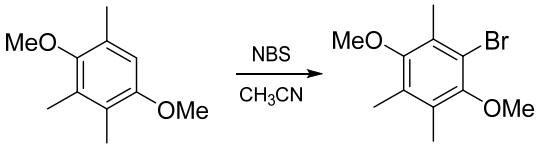


365

The compound was prepared according to a method adapted from the literature.[397] To a solution of 1,4-dihydroxy-2,3-dimethylbenzene (6.03 g, 36.3 mmol) in acetone (60

mL) was added K_2CO_3 (20.0 g, 145 mmol) and MeI (9.00 mL, 145 mmol) under nitrogen, and the mixture was stirred for 48 hours at reflux temperature. The solvent was removed *in vacuo*, water was added and the compound was extracted with Et_2O. The combined organic layers were washed with water and dried over Na_2SO_4, the solvent was removed *in vacuo* and the residue was purified by column chromatography (95:5 petroleum ether/Et_2O) to yield product as a white solid (5.42 g, 79%). ν (cm^{-1}); 2952 (C-H stretch), 1094 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.76 (2H, s, H_5 and H_6), 3.89 (6H, s, OCH_3), 2.32 (6H, s, Ph-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4 (C_1 and C_4), 126.1 (C_2 and C_3), 107.2 (C_5 and C_6), 55.3 (OCH_3), 11.52 (CH_3); LRMS (ESI) *m/z*: calcd. for $C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.1, found 189.2; m.p = 78-79 °C. Spectroscopic data are consistent with that previously reported.[438]

1-Bromo-2,5-dimethoxy-3,4,6-trimethylbenzene 370

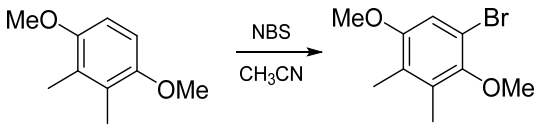


364 **370**

The compound was prepared according to a literature procedure.[415] To a solution of 1,4-dimethoxy-2,3,5-trimethylbenzene **364** (0.36 g, 2.0 mmol) in CH_3CN (10 mL) was added *N*-bromosuccinimide (0.53 g, 3.0 mmol) and the mixture was stirred at room temperature for 2.5 hours. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, washed with water and brine and dried over Na_2SO_4 to yield product as an off-white solid which was used without further purification (0.50 g, 97%). ν (cm^{-1}); 2935 (alkyl C-H stretch), 1222 (C-O stretch), 753 (C-Br stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 2.35 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.17 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.6 (Ph-C), 151.1 (Ph-C), 150.6 (Ph-C), 129.1 (Ph-C), 129.0 (Ph-C), 117.0 (Ph-C), 59.72 (OCH_3),

59.61 (OCH_3), 15.93 (CH_3), 13.19 (CH_3), 12.50 (CH_3); LRMS (ESI) *m*/*z*: calcd. for $C_{11}H_{15}{}^{79}BrNaO_2$ $[M+Na]^+$ 281.0, found 281.0; m.p = 70-71 °C. Spectroscopic data are consistent with that previously reported.[415, 439]

1-Bromo-2,5-dimethoxy-3,4-dimethylbenzene 371

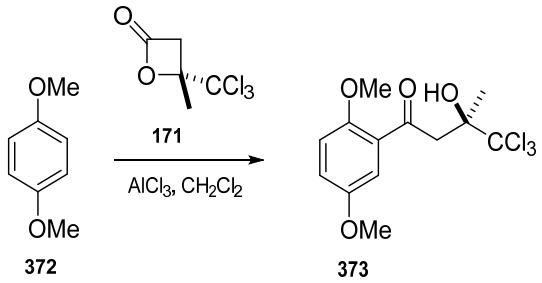


365 **371**

The compound was prepared according to a literature procedure.[415] To a solution of 1,4-dimethoxy-2,3-dimethylbenzene **365** (0.20 g, 1.2 mmol) in CH_3CN (5 mL) was added *N*-bromosuccinimide (NBS) (0.32 g, 1.8 mmol) and the mixture was stirred at room temperature for 45 minutes. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, washed with water and brine and dried over Na_2SO_4 to yield product to yield product as a pale yellow oil (292 mg, 91%) after column chromatography (95:5 petroleum ether/Et_2O). ν (cm^{-1}); 3018 (C-H stretch), 1214 (C-O stretch), 751 (C-H bend); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.86 (1H, s, Ph-H), 3.76 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.23 (3H, s, CH_3), 2.08 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5 (Ph-C), 148.7 (Ph-C), 131.7 (Ph-C), 125.2 (Ph-C), 112.8 (Ph-C), 111.7 (Ph-CH), 59.9 (OCH_3), 55.3 (OCH_3), 12.7 (CH_3), 11.5 (CH_3); LRMS (ESI) *m*/*z*: calcd. for $C_{10}H_{13}{}^{79}BrNaO_2$ $[M+Na]^+$ 267.0, found 267.1. Spectroscopic data are consistent with that previously reported.[438]

(*R*)-4,4,4-Trichloro-1-(2',5'-dimethoxyphenyl)-3-hydroxy-3-methylbutan-1-one

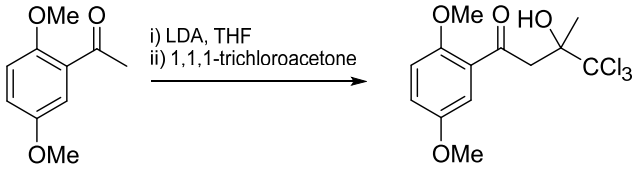
373



The compound was prepared according to a procedure adapted from the literature.[395] To a solution of $AlCl_3$ (0.632g, 4.75 mmol) and 1,4-dimethoxybenzene **372** (1.38g, 10 mmol) in CH_2Cl_2 (10 mL) was added a solution of (*R*)-(+)-4-methyl-4-(trichloromethyl)-2-oxetanone **171** (0.203g, 1.00 mmol) in CH_2Cl_2 (2 mL), at 0 °C. The mixture was warmed to room temperature and stirred overnight. The resulting solution was then cooled to 0 °C, quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2. The organic fractions were washed with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (95:5 petroleum ether/EtOAc to 1:1) to yield product as a yellow solid (0.292 g, 85%, ≥ 98% *e.e.*). ν (cm^{-1}); 3444 (br, O-H stretch), 1647 (C=O stretch), 1278 and 1030 (C-O stretch), 794.9 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (1H, d, *J* 3, H_6'), 7.10 (1H, dd, *J* 9.5, 3, H_4'), 6.95 (1H, d, *J* 9, H_3'), 5.49 (1H, s, OH), 3.92 (3H, s, OCH_3), 3.83 (1H, d, *J* 16, C*H*HCO), 3.81 (3H, s, OCH_3), 3.64 (1H, d, *J* 16.5, CH*H*CO), 1.72 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.7 (CO), 153.7 (C_5'), 153.3 (C_2'), 127.9 (C_1'), 121.6 (C_4'), 114.0 (C_6'), 113.4 (C_3'), 108.0 (CCl_3), 82.7 (C(OH)), 56.2 (OCH_3), 55.9 (OCH_3), 46.7 (CH_2), 23.4 (C(*C*H_3)); HRMS (ESI) *m/z*: calcd. for $C_{13}H_{15}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 362.9928, found 362.9931; m.p = 89-91 °C; $[\alpha]_D^{30}$ +7.7 (*c* 1, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC (Daicel

Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min, 227 nm, (*R*) isomer 14.81 min, (*S*) isomer 16.33 min).

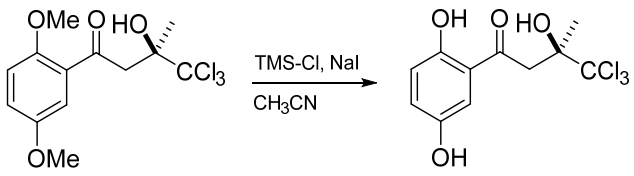
4,4,4-Trichloro-1-(2',5'-dimethoxyphenyl)-3-hydroxy-3-methylbutan-1-one (±)-373



381 (±)-**373**

A solution of diisopropylamine (1.40 mL, 10.0 mmol) in dry Et_2O (20 mL) was cooled to -78 °C and *n*-BuLi (3.60 mL, 9.16 mmol) was added dropwise. After stirring for 30 minutes at this temperature, 1-(2',5'-dimethoxyphenyl)ethan-1-one **381** (1.35 mL, 8.54 mmol) was added dropwise over 20 minutes. After stirring for one hour 1,1,1-trichloroacetone (1.41 mL, 12.5 mmol) was added slowly over 20 minutes and the mixture was stirred at -78 °C for a further three hours, before warming to room temperature and stirring overnight. The reaction was quenched with saturated NH_4Cl (aq.) (20 mL), extracted with Et_2O and the organic fractions were washed with water and brine. The solvent was removed *in vacuo* and the residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as an off-white solid (1.63 g, 56%). ν (cm^{-1}); 3407 (br, O-H stretch), 1643 (C=O stretch), 1261 and 1091 (C-O stretch), 787 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (1H, d, *J* 3, H_6'), 7.09 (1H, dd, *J* 9, 3, H_4'), 6.95 (1H, d, *J* 9, H_3'), 5.98 (1H, s, OH), 3.91 (3H, s, OCH_3), 3.84 (1H, d, *J* 17, C*H*HCO), 3.80 (3H, s, OCH_3) 3.63 (1H, d, *J* 16.5, CH*H*CO), 1.71 (3H, s, C_3-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.7 (CO), 153.7 (C_5'), 153.2 (C_2'), 127.9 (C_1'), 121.6 (C_4'), 114.0 (C_6'), 113.4 (C_3'), 108.0 (CCl_3), 82.7 (C(OH)), 56.2 (C_2'-O*C*H_3), 55.9 (C_5'-O*C*H_3), 46.7 (CH_2), 23.4 (C(*C*H_3)); HRMS (ESI) *m*/*z*: calcd. for $C_{13}H_{15}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 362.9928, found 362.9925; m.p = 105-106 °C.

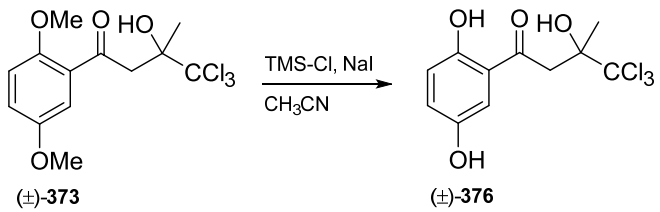
(*R*)-4,4,4-Trichloro-1-(2',5'-dihydroxyphenyl)-3-hydroxy-3-methylbutan-1-one 376



373 **376**

The compound was prepared according to a procedure adapted from the literature.[400] To a solution of (*R*)-4,4,4-trichloro-1-(2',5'-dimethoxyphenyl)-3-hydroxy-3-methylbutan-1-one **373** (0.751g, 2.20 mmol) and sodium iodide (1.98g, 13.2 mmol) in dry CH_3CN (10 mL) was added chlorotrimethylsilane (1.44g, 13.2 mmol), slowly with continuous stirring under nitrogen. The reaction mixture was heated to 70 °C for 60 hours, before being quenched with water and extracted with Et_2O. The organic layer was washed with 5% sodium thiosulfate (aq.), brine and dried over Na_2SO_4. The residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as a yellow crystalline solid (0.225 g, 33%). ν (cm^{-1}); 3360 (br, O-H stretch), 1644 (C=O stretch), 1186 (C-O stretch), 775 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.6 (1H, s, C_2'-OH), 7.25 (1H, d, *J* 3, H_6'), 7.10 (1H, dd, *J* 9, 3, H_4'), 6.94 (1H, d, *J* 9, H_3'), 4.84 (1H, s, C_5'-OH), 4.97 (1H, s, C_3-OH), 3.77 (1H, d, *J* 15.5, C*H*HCO), 3.44 (1H, d, *J* 15.5, CH*H*CO), 1.77 (3H, s, $C(CH_3)$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6 (CO), 157.4 (C_2'), 147.6 (C_5'), 126.6 (C_4'), 119.9 (C_3'), 119.8 (C_1'), 114.9 (C_6'), 107.6 (CCl_3), 82.4 ($C(CH_3)$), 41.8 (CH_2), 25.3 (CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{11}H_{11}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 334.9615, found 334.9620; m.p = 135-136 °C; $[\alpha]_D{}^{30}$ +17.8 (*c* 0.64, $CHCl_3$).

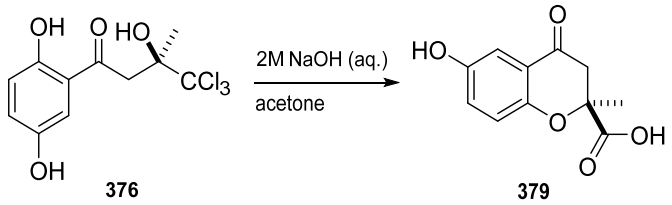
4,4,4-Trichloro-1-(2',5'-dihydroxyphenyl)-3-hydroxy-3-methylbutan-1-one (±)-376



(±)-**373** (±)-**376**

The compound was prepared according to a procedure adapted from the literature.[400] To a solution of 4,4,4-trichloro-1-(2',5'-dimethoxyphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**373** (0.120 g, 0.351 mmol) and sodium iodide (0.317 g, 2.11 mmol) in dry CH_3CN (5 mL) was added chlorotrimethylsilane (0.269 g, 2.11 mmol), slowly with continuous stirring under nitrogen. The reaction mixture was heated to 70 °C for 60 hours, before being quenched with water and extracted with Et_2O. The organic layer was washed with 5% sodium thiosulfate (aq.), brine and dried over Na_2SO_4. The residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as a yellow crystalline solid (61 mg, 55%). ν (cm^{-1}); 3363 (br, O-H stretch), 1640 (C=O stretch), 1181 (C-O stretch), 780 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.55 (1H, s, C_2'-OH), 7.25 (1H, d, *J* 3, H_6'), 7.10 (1H, dd, *J* 9, 3, H_4'), 6.93 (1H, d, *J* 9, H_3'), 4.97 (1H, s, C_5'-OH), 4.49 (1H, s, C_3-OH), 3.77 (1H, d, *J* 15.5, C*H*HCO), 3.44 (1H, d, *J* 15.5, CH*H*CO), 1.77 (3H, s, C(CH_3)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.7 (CO), 157.4 (C_2'), 147.7 (C_5'), 126.3 (C_4'), 119.8 (C_3'), 119.5 (C_1'), 115.1 (C_6'), 107.6 (CCl_3), 82.4 (*C*(CH_3)), 41.8 (CH_2), 23.5 (CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{11}H_{11}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 334.9615, found 334.9615; m.p = 127-128 °C.

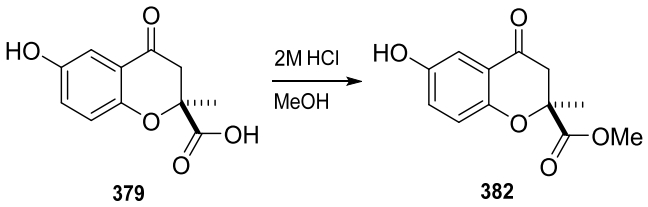
Methyl (*S*)-6-hydroxy-2-methyl-4-oxochromane-2-carboxylate 379



376 379

To a deoxygenated solution of (*R*)-4,4,4-trichloro-1-(2',5'-dihydroxyphenyl)-3-hydroxy-3-methylbutan-1-one **376** (0.340 g, 1.08 mmol) in acetone (10 mL) was added deoxygenated 2M NaOH (aq.) (2.17 mL, 4.33 mmol) and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield crude product as a brown crystalline solid which was used without further purification (0.140 g, 58%). A sample was purified by column chromatography (8:2:0.1 EtOAc/MeOH/AcOH) for analysis. ν (cm^{-1}): 3217 (br, O-H stretch), 1675 (C=O stretch), 1213 (C-O stretch); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 7.02-6.96 (2H, m, Ar-H), 6.89 (1H, d, *J* 8.5, H_8), 2.98 (1H, d, *J* 16.5, C*H*HCO), 2.89 (1H, d, *J* 17, CH*H*CO), 1.56 (3H, s, $C(CH_3)$); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 191.3 (CO), 173.9 (CO_2), 154.1 (C_6), 151.8 (C_{8a}), 124.9 (C_8), 120.8 (C_{4a}), 119.54 (C_7), 110.0 (C_5), 81.7 ($C(CH_3)$), 45.9 (CH_2), 25.2 ($C(CH_3)$); HRMS (ESI) *m*/*z*: calcd. for $C_{11}H_9O_5$ $[M-H]^-$ 221.0455, found 221.0456; m.p = 141-142 °C; $[\alpha]_D^{30}$ +45 (*c* 0.80, $CHCl_3$).

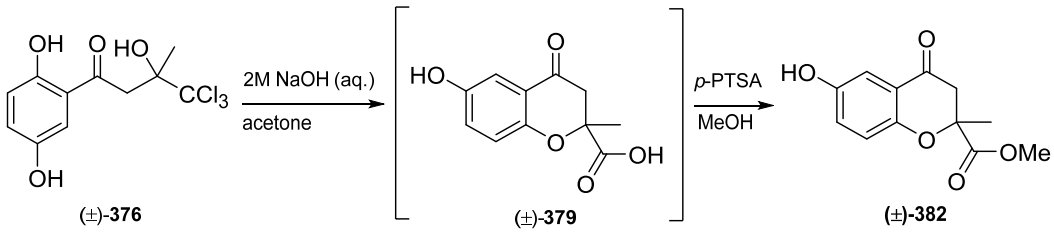
Methyl (*S*)-6-hydroxy-2-methyl-4-oxochromane-2-carboxylate 382



379 382

A solution of (*S*)-6-hydroxy-2-methyl-4-oxochromane-2-carboxylic acid **379** (20 mg, 0.1 mmol) in 2M methanolic HCl (5 mL) was stirred at room temperature for 16 hours. After this time the mixture was concentrated *in vacuo* and the residue was taken up with EtOAc, washed with saturated $NaHCO_3$ (aq.), water, and dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting residue was purified by column chromatography (1:1 petroleum ether/EtOAc) to yield product as a white solid (21 mg, 90%, ≥ 98% *e.e.*). ν (cm^{-1}); 3413 (br, O-H stretch), 1737 (ester C=O stretch), 1683 (ketone C=O stretch), 1199 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (1H, d, *J* 3, H_5), 7.08 (1H, dd, *J* 9, 3, H_7), 6.98 (1H, d, *J* 9, H_8), 5.63 (1H, s, OH), 3.68 (3H, s, OCH_3), 3.19 (1H, d, *J* 16.5, C*H*HCO), 2.85 (1H, d, *J* 17, CH*H*CO), 1.71 (3H, s, $C(CH_3)$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.6 (CO), 172.3 (CO_2), 154.0 (C_6), 150.5 (C_{8a}), 125.2 (C_7), 120.4 (C_{4a}), 119.5 (C_8), 111.0 (C_5), 81.4 (*C*(CH_3)), 53.1 (OCH_3), 45.5 (CH_2), 24.9 (C(*C*H_3)); HRMS (ESI) *m*/*z*: calcd. for $C_{12}H_{12}NaO_5$ $[M+Na]^+$ 259.0577, found 259.0579; m.p = 150-151 °C; $[\alpha]_D^{25}$ +49.6 (*c* 0.50, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel AD-H column, 2-propanol : hexane = 10 : 90, 1 mL/min, 227 nm, (*R*) isomer 14.35 min, (*S*) isomer 16.12 min).

Methyl 6-hydroxy-2-methyl-4-oxochromane-2-carboxylate (±)-382

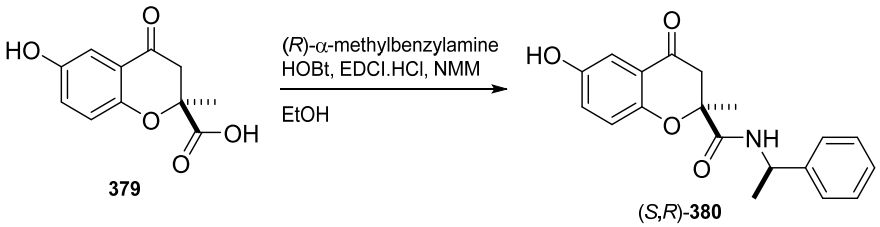


To a deoxygenated solution of 4,4,4-trichloro-1-(2',5'-dihydroxyphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**376** (60.0 mg, 0.192 mmol) in acetone (2.5 mL) was added deoxygenated 2M NaOH (aq.) (0.382 mL, 0.764 mmol) and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield (±)-**379** as a brown crystalline solid, which was used straight away in the next step without further purification. A sample was purified by column chromatography (8:2:0.1 EtOAc/MeOH/AcOH) for analysis. ν (cm^{-1}); 3272 (br, O-H stretch), 1674 (C=O stretch), 1212 (C-O stretch); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 6.96 (1H, d, *J* 3, H_5), 6.91 (1H, dd, *J* 9, 3, H_7), 6.80 (1H, d, *J* 9, H_8), 3.00 (1H, d, *J* 16, C*H*HCO), 2.62 (1H, d, *J* 16, CH*H*CO), 1.45 (3H, s, CH_3); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 192.5 (CO), 174.3 (CO_2), 155.2 (C_6), 151.0 (C_{8a}), 124.2 (C_8), 121.2 (C_{4a}), 119.4 (C_7), 109.9 (C_5), 82.8 (*C*(CH_3)), 47.0 (CH_2), 25.9 (C(*C*H_3)); HRMS (ESI) *m*/*z*: calcd. for $C_{11}H_9O_5$ $[M-H]^-$ 221.0455, found 221.0460; m.p = 163-164 °C.

To a solution of crude 6-hydroxy-2-methyl-4-oxochromane-2-carboxylic acid (±)-**379** (20 mg, 0.10 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid (PTSA) (20 mg, 0.10 mmol), and the solution was stirred at reflux temperature for six hours. After cooling to room temperature the solvent was removed *in vacuo* and the residue was taken up with EtOAc. The organic fraction was washed with saturated $NaHCO_3$ (aq.)

and water and dried over Na_2SO_4. The residue was purified by column chromatography (1:1 petroleum ether/EtOAc) to yield product as an off-white white solid (21 mg, 39% from (±)-**376**). ν (cm^{-1}); 3389 (br, O-H stretch), 1744 (ester C=O stretch), 1680 (ketone C=O stretch), 1196 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (1H, d, *J* 3, H_5), 7.08 (1H, dd, *J* 9, 3, H_7), 6.97 (1H, d, *J* 9, H_8), 6.15 (1H, s, OH), 3.68 (3H, s, OCH_3), 3.20 (1H, d, *J* 17, C*H*HCO), 3.86 (1H, d, *J* 17, CH*H*CO), 1.71 (3H, s, $C(CH_3)$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.0 (CO), 172.4 (CO_2), 154.5 (C_6), 150.7 (C_{8a}), 125.4 (C_7), 120.3 (C_{4a}), 119.5 (C_8), 111.0 (C_5), 81.39 ($C(CH_3)$), 53.10 (OCH_3), 45.50 (CH_2), 24.89 ($C(CH_3)$); HRMS (ESI) *m*/*z*: calcd. for $C_{12}H_{12}NaO_5$ $[M+Na]^+$ 259.0577, found 259.0582; m.p = 180-181 °C.

(*S*,*R*)-6-Hydroxy-2-methyl-4-oxo-*N*-[1-phenylethyl]chromane-2-carboxamide 380



To a solution of (*S*)-6-hydroxy-2-methyl-4-oxochromane-2-carboxylic acid **379** (30.0 mg, 0.135 mmol) in EtOH (5 mL) was added (*R*)-α-methylbenzylamine (24.0 mg, 0.203 mmol), HOBt (18.0 mg, 0.135 mmol), EDCI.HCl (53.0 mg, 0.338 mmol) and NMM (50.0 µL, 0.473 mmol) and the mixture was stirred overnight at room temperature. The resulting mixture was partitioned between pH 2 buffer and EtOAc, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (8:2 petroleum ether/EtOAc to 1:1) to yield product as a white solid (20 mg, 30%). ν (cm^{-1}); 3337 (br, N-H stretch), 1683 (ketone C=O stretch), 1643 (amide C=O stretch), 1205 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (1H, d,

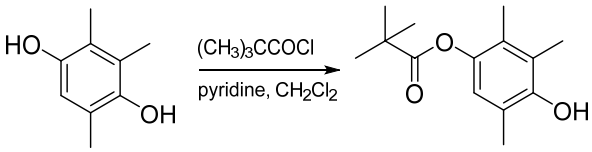
J 3, H_5), 7.23-7.16 (3H, m, Ph-H), 7.04 (1H, dd, *J* 9, 3, H_7), 6.98-6.93 (2H, m, Ph-H), 6.90 (1H, d, *J* 9.0, H_8), 6.62 (1H, d, *J* 8.0, NH), 5.26 (1H, s, OH), 5.05 (1H, dq, *J* 8, 7, NHC*H*), 3.20 (1H, d, *J* 17, C*H*HCO), 2.81 (1H, d, *J* 17, CH*H*CO), 1.65 (3H, s, C(CH_3)), 1.50 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.2 (CO), 171.0 (CONH), 153.0 (C_6), 150.7 (C_{8a}), 142.4 (Ph-C), 129.0 (Ph-C), 127.3 (Ph-C), 125.7 (Ph-C), 124.6 (C_7), 121.1 (C_{4a}), 119.1 (C_8), 111.5 (C_5), 82.42 (*C*(CH_3)), 48.46 (NHCH), 44.77 (CH_2), 24.05 (C(*C*H_3)), 21.52 (CH*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{19}H_{20}NO_4$ $[M+H]^+$ = 326.1387, found 326.1389; m.p = 190-191 °C.

(*S*,*S*)-6-Hydroxy-2-methyl-4-oxo-*N*-[1-phenylethyl]chromane-2-carboxamide 380

To a solution of (*S*)-6-hydroxy-2-methyl-4-oxochromane-2-carboxylic acid **379** (60.0 mg, 0.270 mmol) in EtOH (5 mL) was added (*S*)-α-methylbenzylamine (65.0 mg, 0.540 mmol), HOBt (36.0 mg, 0.270 mmol), EDCI.HCl (105 mg, 0.675 mmol) and NMM (0.104 mL, 0.945 mmol) and the mixture was stirred overnight at room temperature. The resulting mixture was partitioned between pH 2 buffer and EtOAc, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (8:2 petroleum ether/EtOAc to 1:1) to yield product as a colourless oil (20 mg, 23%). ν (cm^{-1}); 3330 (br, N-H stretch), 1679 (ketone C=O stretch), 1650 (amide C=O stretch), 1215 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.32 (3H, m, Ar-H), 7.31-7.27 (3H, m, Ar-H), 7.10 (1H, dd, *J* 9, 3, H_7), 6.94 (1H, d, *J* 9, H_8), 6.68 (1H, d, *J* 8, NH), 5.74 (1H, s, OH), 5.04 (1H, dq, *J* 8, 7, NHC*H*), 3.22 (1H,

d, *J* 17, C*H*HCO), 2.86 (1H, d, *J* 17, CH*H*CO), 1.59 (3H, s, C(CH_3)), 1.33 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.5 (CO), 171.1 (CONH), 152.8 (C_6), 150.9 (C_{8a}), 142.6 (Ph-C), 128.3 (Ph-C), 127.6 (Ph-C), 126.0 (Ph-C), 124.8 (C_7), 121.0 (C_{4a}), 119.0 (C_8), 111.6 (C_5), 82.3 (C_2), 48.7 (NHCH), 44.8 (CH_2), 23.7 (C(*C*H_3)), 21.6 (CH*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{19}H_{20}NNaO_4$ $[M+H]^+$ 348.1206, found 348.1205; m.p = 60-61 °C.

4-Hydroxy-2,3,5-trimethylphenyl pivalate 383

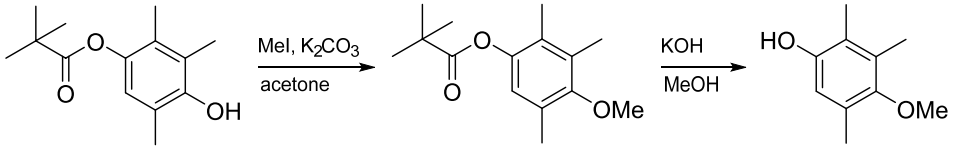


383

The compound was prepared according to a literature procedure.[216] To a suspension of trimethylhydroquinone (5.00 g, 32.9 mmol) in CH_2Cl_2 (40 mL) was added pyridine (8.33 mL, 105 mmol) and the mixture was cooled to 0 °C. Pivaloyl chloride (4.25 mL, 34.5 mmol) in CH_2Cl_2 (20 mL) was then added dropwise over 45 minutes and the solution was stirred at room temperature for an additional 18 hours, after which time it was washed with 2M HCl (aq.), 5% $NaHCO_3$ (aq.) and brine. The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield crude product as an orange solid (7.04 g). This solid was recrystallised in petroleum ether to give product as a white crystalline solid (4.81 g, 62%). ν (cm^{-1}); 3490 (br, O-H stretch), 1730 (C=O stretch), 1135 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (1H, s, Ph-H), 5.00 (1H, s, OH), 2.12 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.39 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3 (CO_2), 149.2 (Ar-C), 141.7 (Ar-C), 126.5 (Ar-C), 123.2 (Ar-C), 120.5 (Ar-C), 120.0 (Ar-C), 38.6 (*C*(CH_3)$_3$), 26.7 (C(*C*H_3)$_3$), 15.3 (Ar-CH_3), 12.0 (Ar-CH_3), 11.6 (Ar-CH_3); LRMS (ESI) *m*/*z*: calcd. for

$C_{14}H_{20}NaO_3$ $[M+Na]^+$ 259.1, found 259.1; m.p = 123-124 °C. Spectroscopic data are consistent with that previously reported.[216]

4-Methoxy-2,3,5-trimethylphenol 384



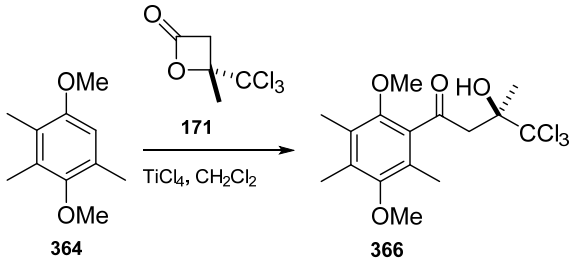
383 **384**

The compound was prepared according to a literature procedure.[216] To a solution of 4-hydroxy-2,3,5-trimethylphenyl 2,2-dimethylpropanoate **383** (14.2 g, 60.3 mmol) in acetone (150 mL) was added K_2CO_3 (16.7 g, 121 mmol) and MeI (11.3 mL, 181 mmol) under nitrogen, and the mixture was stirred at reflux temperature for 48 hours. After cooling to room temperature, the solids were filtered off and washed with acetone, the filtrate was removed *in vacuo* and the residue was taken up in Et_2O. The organic layer was washed with saturated Na_2CO_3 (aq.), water and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield the methyl ether as an orange oil (12.7 g, 84%), which was used directly in the next step without further purification. ν (cm^{-1}); 2973 (C-H stretch), 1746 (C=O stretch), 1117 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.65 (1H, s, Ph-H), 3.68 (3H, s, OCH_3), 2.25 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.38 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2 (CO_2), 154.4 (Ar-C), 145.1 (Ar-C), 130.9 (Ar-C), 128.8 (Ar-C), 127.4 (Ar-C), 121.0 (Ar-C), 60.0 (OCH_3), 39.1 ($C(CH_3)_3$), 27.4 ($C(CH_3)_3$), 16.0 (Ar-CH_3), 12.7 (Ar-CH_3), 12.6 (Ar-CH_3); LRMS (ESI) *m/z*: calcd. for $C_{15}H_{22}NaO_3$ $[M+Na]^+$ 273.1, found 272.8. Spectroscopic data are consistent with that previously reported.[216]

To a solution of 4-methoxy-2,3,5-trimethylphenyl pivalate (5.0 g, 20 mmol) in MeOH (30 mL) was added a solution of KOH (1.8 g, 32 mmol) in water (10 mL) and the mixture was stirred at reflux temperature for six hours, then at room temperature

overnight. The solvent was then removed *in vacuo* and the residue was diluted with water and acidified with 2M HCl (aq.). The aqueous layer was extracted with Et_2O and the organic fractions were washed with saturated Na_2CO_3 (aq.), brine and dried over Na_2SO_4 to give crude product as a dark brown oil. Further purification by column chromatography (8:2 petroleum ether/EtOAc) yielded product as a yellow solid after drying under high vacuum (3.14 g, 95%). ν (cm^{-1}); 3404 (br, O-H stretch), 1224 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.43 (1H, s, Ph-H), 5.44 (1H, s, OH), 3.69 (3H, s, OCH_3), 2.23 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.15 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.3 (Ar-C), 149.7 (Ar-C), 130.7 (Ar-C), 128.3 (Ar-C), 121.4 (Ar-C), 114.6 (Ar-C), 60.8 (OCH_3), 16.0 (Ar-CH_3), 12.7 (Ar-CH_3), 11.9 (Ar-CH_3); LRMS (ESI) *m/z*: calcd. for $C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.1, found 189.0; m.p = 50-51 °C. Spectroscopic data are consistent with that previously reported.[216]

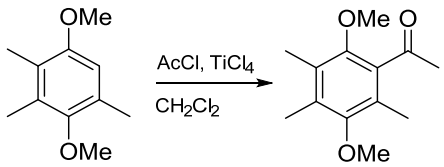
(*R*)-4,4,4-Trichloro-1-(2',5'-dimethoxy-3',4',6'-trimethylphenyl)-3-hydroxy-3-methylbutan-1-one 366



A solution of 1,4-dimethoxy-2,3,5-trimethylbenzene (14.0 g, 77.8 mmol) **364** in CH_2Cl_2 (30 mL) was cooled to 0 °C and $TiCl_4$ (3.11 mL, 28.3 mmol) was added dropwise under nitrogen. After stirring for five minutes, (*R*)-(+)-4-methyl-4-(trichloromethyl)-2-oxetanone **171** (1.58 g, 7.78 mmol) dissolved in minimum CH_2Cl_2 was added dropwise and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2, the combined organic fractions were washed with water and brine and dried over Na_2SO_4.

The solvent was removed *in vacuo* and the resulting residue was purified by column chromatography (95:5 petroleum ether/EtOAc to 8:2) to yield product as a yellow oil (2.40 g, 80 %). ν (cm^{-1}); 3437 (br, O-H stretch), 1688 (C=O stretch), 1259 and 1082 (C-O stretch), 791 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.93 (1H, s, OH), 3.67 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.56-3.50 (2H, m, CH_2), 2.22 (3H, s, Ar-CH_3), 2.17 (6H, s, Ar-CH_3), 1.81 (3H, s, C_3-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.9 (CO), 153.4 (C_5'), 150.8 (C_2'), 133.6 (C_4'), 129.8 (C_6'), 129.1 (C_3'), 125.2 (C_1'), 107.3 (CCl_3), 81.8 (C(OH)), 62.5 (C_2'-O*C*H_3), 60.2 (C_5'-O*C*H_3), 49.0 (CH_2), 23.3 (C_3-*C*H_3), 13.04 (Ar-CH_3), 12.39 (2 x Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{21}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 405.0398, found 405.0397; $[\alpha]_D{}^{25}$ -0.6 (*c* 12.56, $CHCl_3$).

1-(2',5'-Dimethoxy-3',4',6'-trimethylphenyl)ethan-1-one 388

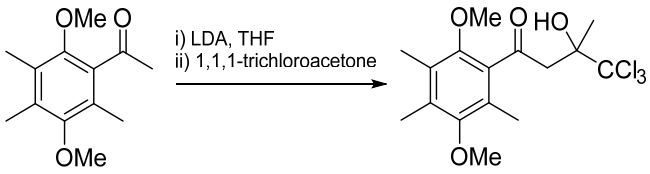


364 **388**

A solution of 1,4-dimethoxy-2,3,5-trimethyl benzene **364** (11.6 g, 64.4 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and $TiCl_4$ (2.12 mL, 19.3 mmol) was added under nitrogen. After stirring for 10 minutes, acetyl chloride (0.460 mL, 6.44 mmol) was added dropwise and the solution was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (97.5:2.5 petroleum ether/EtOAc to 8:2) to yield the product as a yellow oil (0.910 g, 64%). ν (cm^{-1}); 1697 (C=O stretch), 1269 and 1084 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.65 (3H, s, C_5'-OCH_3), 3.63 (3H, s, C_2'-OCH_3), 2.50 (3H, s, $COCH_3$), 2.20 (3H, s, C_4'-CH_3), 2.16 (3H, s, C_3'-CH_3), 2.14 (3H, s, C_6'-CH_3);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.8 (CO), 153.2 (C_5'), 150.2 (C_2'), 134.8 (C_1'), 132.1, 128.7 (C_3'and C_4'), 124.5 (C_6'), 62.2 (C_2'-O*C*H$_3$), 60.1 (C_5'-O*C*H$_3$), 32.4 (CO*C*H$_3$), 12.9 (Ar-CH$_3$), 12.3 (2 x Ar-CH$_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 245.1151.

4,4,4-Trichloro-1-(2',5'-dimethoxy-3',4',6'-trimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-366

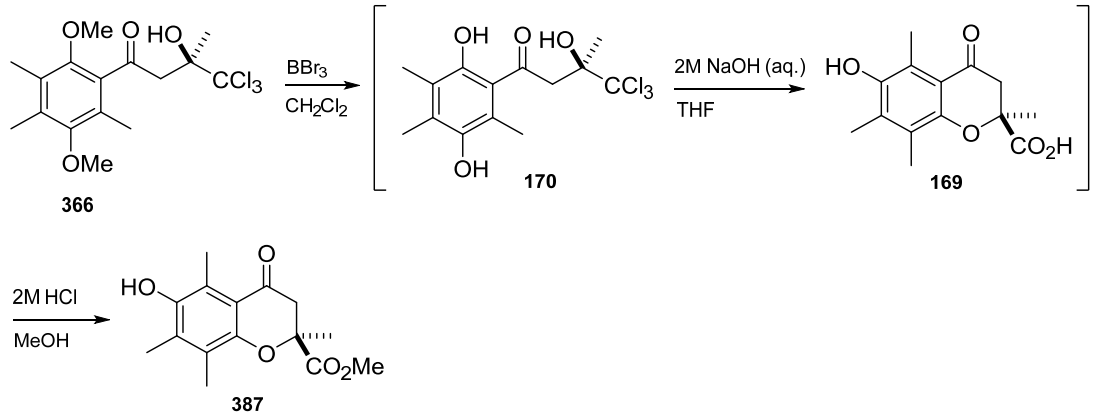


368 **(±)-366**

A solution of diisopropylamine (0.680 mL, 4.86 mmol) in dry Et_2O (20 mL) was cooled to -78 °C and *n*-BuLi (2.5 M, 1.78 mL, 4.46 mmol) was added dropwise. After stirring for 30 minutes at this temperature, 1-(2',5'-dimethoxy-3',4',6'-trimethylphenyl)ethan-1-one **368** (0.900 g, 4.05 mmol) was added dropwise over 20 minutes. After stirring for one hour 1,1,1-trichloroacetone (0.685 mL, 6.08 mmol) was added slowly over 20 minutes and the mixture was stirred at -78 °C for a further three hours, before warming to room temperature and stirring overnight. The reaction was quenched with saturated NH_4Cl (aq.) (20 mL), extracted with Et_2O and the organic fractions were washed with water and brine. The solvent was removed *in vacuo* and the residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as an orange solid (0.630 g, 41%) after column chromatography (85:15 petroleum ether/Et_2O). ν (cm^{-1}); 3485 (br, O-H stretch), 1687 (C=O stretch), 1180 and 1075 (C-O stretch), 777 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.98 (1H, s, OH), 3.66 (3H, s, C_5'-OCH$_3$), 3.65 (3H, s, C_2'-OCH$_3$), 3.55-3.52 (2H, m, CH_2), 2.22 (3H, s, Ar-CH$_3$), 2.18-2.15 (6H, m, Ar-CH$_3$), 1.80 (3H, s, C_3-CH$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.7 (CO), 153.4 (C_5'), 150.8 (C_2'), 133.5 (C_4'), 129.4, 129.2 (C_6' and

C_3'), 125.2 (C_1'), 107.2 (CCl_3), 83.8 (C(OH)), 62.5 (C_2'-O*C*H_3), 60.2 (C_5'-O*C*H_3), 48.9 (CH_2), 23.3 (C_3-*C*H_3), 13.1 (Ar-CH_3), 12.4 (2 x Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{22}{}^{35}Cl_3O_4$ $[M+H]^+$ 383.0578, found 383.0575; m.p = 87-88 °C.

Methyl (*S*)-6-hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylate 387



To a solution of (*R*)-4,4,4-trichloro-1-(2',5'-dimethoxy-3',4',6'-trimethylphenyl)-3-hydroxy-3-methylbutan-1-one **366** (0.910 g, 2.37 mmol) in dry CH_2Cl_2 (20 mL) was added BBr_3 (0.900 mL, 9.48 mmol) at -78 °C under nitrogen, and the mixture was warmed to room temperature and stirred overnight. After this time the reaction was quenched with water and the solvent was removed under a flow of nitrogen. To obtain the best yields the crude mixture of hydroquinone **170** was reacted immediately in the next step. A sample could be prepared for analysis by column chromatography (8:2 petroleum ether/EtOAc). ν (cm^{-1}); 3447 (br, O-H stretch), 1648 (C=O stretch), 1295 (C-O stretch), 795 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.88 (1H, s, C_2'-OH), 5.19 (1H, s, C_3-OH), 4.36 (1H, s, C_5'-OH), 3.61 (1H, d, *J* 15.5, C*H*HCO,), 3.52 (1H, d, *J* 16, CH*H*CO,), 2.39 (3H, s, C_6'-CH_3), 2.24 (3H, s, C_4'-CH_3), 2.19 (3H, s, C_3'-CH_3), 1.67 (3H, s, C_3-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.0 (CO), 151.8 (C_2'), 145.5 (C_5'), 132.0 (C_4'), 124.0 (C_3'), 122.1 (C_1'), 118.6 (C_6'), 107.2 (CCl_3), 83.0 (C_3), 47.1 (CH_2), 23.5 (C_3-*C*H_3), 15.8 (C_6'-CH_3), 13.3 (C_4'-CH_3), 11.9 (C_3'-CH_3); HRMS

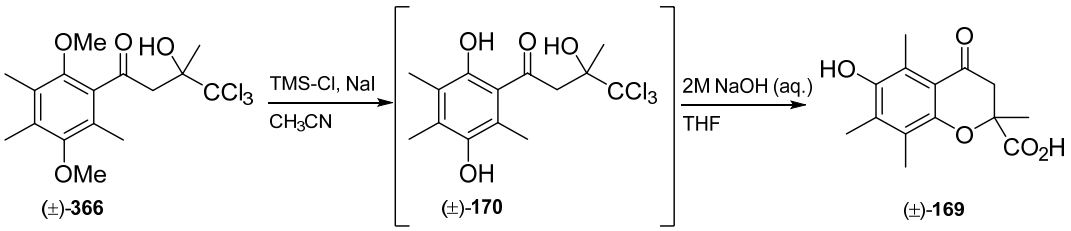
(ESI) *m*/*z*: calcd. for $C_{14}H_{15}Cl_3NaO_4$ $[M+Na]^+$ 374.9928, found 374.9933; $[\alpha]_D^{25}$ -7.1 (*c* 0.28, MeOH).

To a deoxygenated solution of crude (*R*)-4,4,4-trichloro-1-(2',5'-dihydroxy-3',4',6'-trimethylphenyl)-3-hydroxy-3-methylbutan-1-one **170** in THF (15 mL) was added deoxygenated 2M NaOH (aq.) until the solution reached a pH of ≥ 12 (17 mL, 34.0 mmol), and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield product as a brown crystalline solid which was used in the next step without further purification. A sample was purified by column chromatography (8:2:0.1 EtOAc/MeOH/AcOH) for analysis. ν (cm^{-1}); 3389 (br, O-H stretch), 1707 (carboxylic acid C=O stretch), 1628 (ketone C=O stretch), 1207 and 1084 (C-O stretch); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 7.96 (1H, s, C_6-OH), 2.95 (1H, d, *J* 16.5, C*H*HCO), 2.89 (1H, d, *J* 16.5, CH*H*CO), 2.40 (3H, s, C_5-CH_3), 2.17 (3H, s, C_7-CH_3), 2.13 (3H, s, C_8-CH_3), 1.60 (C_2-CH_3); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 193.0 (CO), 174.0 (CO_2), 153.4 (C_{8a}), 147.5 (C_6), 134.3 (C_8), 125.5 (C_5 and C_7), 117.1 (C_{4a}), 80.5 (C_2), 47.4 (CH_2), 25.2 (C_2-*C*H_3), 14.27 (C_5-*C*H_3 and C_7-*C*H_3), 12.52 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{15}O_5$ $[M-H]^-$ 263.0925, found 263.0911; m.p = 194-195 °C; $[\alpha]_D^{25}$ +22.5 (*c* 0.2, MeOH).

Crude (*S*)-6-hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylic acid **169** was dissolved in 2M methanolic HCl (10 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The crude product was purified using column chromatography (8:2 petroleum ether/EtOAc) to yield product as a pale yellow crystalline solid (0.260 g, 42% from

366, ≥ 98% *e.e.*). ν (cm^{-1}); 3532 (br, O-H stretch), 1727 (ester C=O stretch), 1668 (ketone C=O stretch), 1200 and 1086 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.89 (1H, s, C_6-OH), 3.65 (3H, s, CO_2CH_3), 3.16 (1H, d, *J* 16.5, C*H*HCO), 2.83 (1H, d, *J* 16.5, CH*H*CO), 2.50 (3H, s, C_5-CH_3), 2.23 (6H, s, C_7-CH_3 and C_8-CH_3), 1.68 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.7 (CO), 172.9 (CO_2), 153.5 (C_{8a}), 146.8 (C_6), 132.8 (C_7), 124.2 (C_8), 121.2 (C_5), 116.9 (C_{4a}), 80.4 (C_2), 52.8 (CO_2CH_3), 47.3 (CH_2), 25.08 (C_2-CH_3), 13.43 (C_7-CH_3 or C_8-CH_3), 12.94 (C_5-CH_3), 12.04 (C_7-CH_3 or C_8-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{15}H_{18}NaO_5$ $[M+Na]^+$ 301.1046, found 301.1048; m.p = 112-113 °C; $[\alpha]_D^{25}$ +16.3 (*c* 0.04, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 5 : 95, 1 mL/min, 219 nm, (*R*) isomer 29.05 min, (*S*) isomer 31.92 min).

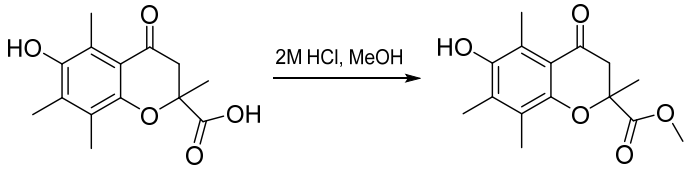
6-Hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylic acid (±)-169



Hydroquinone (±)-**170** was prepared according to a procedure adapted from the literature.[400] To a solution of 4,4,4-trichloro-1-(2',5'-dimethoxy-3',4',6'-trimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**366** (0.751g, 2.20 mmol) and sodium iodide (1.98 g, 13.2 mmol) in dry CH_3CN (10 mL) was added chlorotrimethylsilane (1.44 g, 13.2 mmol), slowly with continuous stirring under nitrogen. The reaction mixture was heated to 70 °C for 60 hours, before being quenched with water and extracted with Et_2O. The organic layer was washed with 5% sodium thiosulfate (aq.), brine and dried over Na_2SO_4. The crude hydroquinone (±)-**170** was not isolated and was used in the next step without further purification. To a deoxygenated solution of crude 4,4,4-trichloro-1-(2',5'-dihydroxy-3',4',6'-

trimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**170** in THF (15 mL) was added deoxygenated 2M NaOH (aq.) until the solution reached a pH of ≥ 12 (17 mL, 34.0 mmol), and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield product as a brown crystalline solid (0.220 g, 37% from (±)-**366**) after column chromatography (100% EtOAc to 8:2:0.1 EtOAC/MeOH/AcOH). ν (cm^{-1}); 3429 (br, O-H stretch), 1714 (acid C=O stretch), 1658 (ketone C=O stretch), 1200 and 1083 (C-O stretch); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 2.94 (1H, d, *J* 16.5, C*H*HCO), 2.86 (1H, d, *J* 16.5, CH*H*CO), 2.40 (3H, s, C_5-CH_3), 2.16 (3H, s, C_7-CH_3), 2.12 (3H, s, C_8-CH_3), 1.58 (3H, s, C_2-CH_3); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 193.2 (CO), 174.1 (CO_2), 153.5 (C_{8a}), 147.5 (C_6), 134.4 (C_8), 123.5, 123.4 (C_7 and C_5), 117.1 (C_{4a}), 80.5 (C_2), 47.4 (CH_2), 25.2 (C_2-*C*H_3), 14.3 (C_7-*C*H_3 and C_5-*C*H_3), 12.5 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{15}O_5$ $[M-H]^-$ 263.0925, found 263.0924; m.p = 70-71 °C.

Methyl 6-hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylate (±)-387

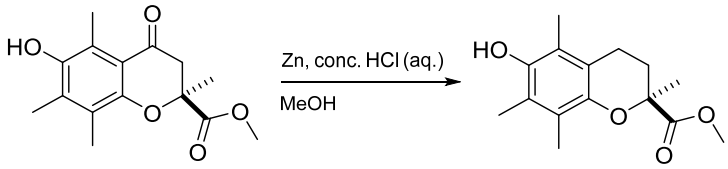


(±)-**169** (±)-**387**

Crude (*S*)-6-hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylic acid (±)-**169** (79 mg, 0.30 mmol) was dissolved in 2M methanolic HCl (10 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The residue was purified by column chromatography (8:2 petroleum ether/EtOAc) to yield product as an off-white solid (60 mg, 72%). ν (cm^{-1});

3529 (br, O-H stretch), 1727 (ester C=O stretch), 1671 (ketone C=O stretch), 1197 and 1091 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.67 (1H, s, OH), 3.65 (3H, s, CO_2CH_3), 3.16 (1H, d, *J* 16.5, C*H*HCO), 2.82 (1H, d, *J* 16.5, CH*H*CO), 2.51 (3H, s, C_5-CH_3), 2.23 (3H, s, C_7-CH_3 or C_8-CH_3), 2.22 (3H, s, C_7-CH_3 or C_8-CH_3), 1.68 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.6 (CO), 172.8 (CO_2), 153.5 (C_{8a}), 146.8 (C_6), 132.6 (C_7), 124.3 (C_8), 121.0 (C_5), 116.9 (C_{4a}), 80.4 (C_2), 52.8 (CO_2CH_3), 47.3 (CH_2), 25.1 (C_2-CH_3), 13.4 (C_7-CH_3 or C_8-CH_3), 12.9 (C_5-CH_3), 12.0 (C_7-CH_3 or C_8-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{15}H_{18}NaO_5$ $[M+Na]^+$ 301.1046, found 301.1047; m.p = 148-149 °C.

Methyl (*S*)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylate 388

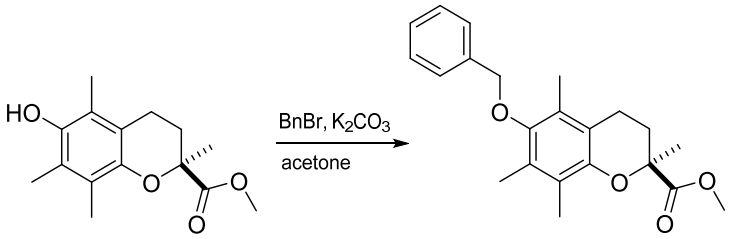


387 **388**

To a solution of methyl (*S*)-6-hydroxy-2,5,7,8-tetramethyl-4-oxochromane-2-carboxylate **387** (0.550 g, 1.98 mmol) in MeOH (25 mL) was added fine zinc powder (1.29 g, 19.8 mmol) and concentrated HCl (4.13 mL, 49.5 mmol) and the mixture was stirred at room temperature for five hours. After filtering through celite, the filtrate was concentrated *in vacuo*. The resulting residue was taken up with Et_2O and washed with brine. The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (85:15 petroleum ether/EtOAc) to yield product as a white solid (0.264 g, 51%). ν (cm^{-1}); 3531 (br, O-H stretch), 1718 (C=O stretch), 1197 and 1103 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.27 (1H, s, OH), 3.67 (3H, s, CO_2CH_3), 2.64 (1H, ddd, *J* 17, 6, 3.5, ArC*H*H), 2.50 (1H, ddd, *J* 17.5, 11.5, 6.5, ArCH*H*), 2.42 (1H, ddd, *J* 13.5, 6.5, 3, $ArCH_2$C*H*H), 2.18 (3H, s, Ar-CH_3), 2.15 (3H, s, Ar-CH_3), 2.05 (3H, s, Ar-CH_3), 1.86

(1H, ddd, *J* 13, 11, 6, $ArCH_2CH\mathit{H}$), 1.60 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (CO_2), 145.5, 145.3 (C_6 and C_{8a}), 122.6, 121.3, 118.4, 116.9 (C_{4a} and C_5 and C_7 and C_8), 77.1 (C_2), 52.4 ($CO_2\mathit{C}H_3$), 30.6 (C_3), 25.4 (C_2-$\mathit{C}H_3$), 21.0 (C_4), 12.2, 11.8, 11.2 (Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1254, found 287.1256; m.p = 134-135 °C; $[\alpha]_D^{25}$ -61.7 (*c* 5, MeOH).

Methyl (*S*)-6-(benzyloxy)-2,5,7,8-tetramethylchromane-2-carboxylate 389

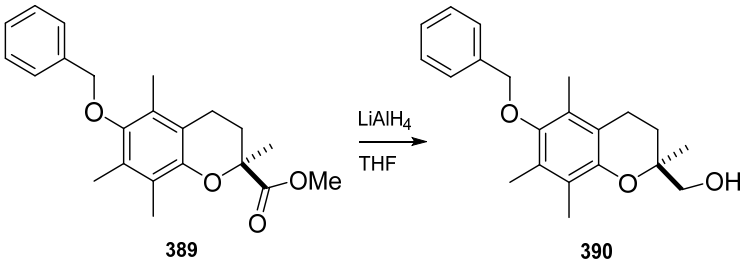


388 **389**

The compound was prepared according to a literature procedure.[140] To a solution of methyl (*S*)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylate **388** (0.150 g, 0.573 mmol) in DMF (2 mL) was added K_2CO_3 (0.119 g, 0.860 mmol) at 0 °C and stirred for 20 minutes. Benzyl bromide (82.0 µL, 0.687 mmol) was then added dropwise and the mixture was stirred at room temperature overnight. The reaction was diluted with water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed thoroughly with water and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (9:1 petroleum ether/EtOAc) to yield product as a white solid (0.193 g, 95%). ν (cm^{-1}); 1747 (C=O stretch), 1253 and 1105 (C-O stretch), 733 and 699 (monosubstituted benzene C-H bend); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.32 (5H, m, Ph-H), 4.70 (2H, s, OCH_2), 3.70 (3H, s, CO_2CH_3), 2.65 (1H, ddd, *J* 17, 6.5, 3.5, ArC*H*H), 2.57-2.40 (2H, m, ArCH*H* and $ArCH_2C\mathit{H}H$), 2.25 (3H, s, C_7-CH_3), 2.20 (3H, s, C_8-CH_3), 2.15 (3H, s, C_5-CH_3), 1.90 (1H, ddd, *J* 12.5, 10.5, 5.5, $ArCH_2CH\mathit{H}$), 1.64 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4 (CO_2), 148.9 (C_6), 147.8

(C_{8a}), 137.8 (Ph-C), 128.5 (Ph-C), 128.3 (C_7 or C_8), 127.8, 127.7 (Ph-C), 126.0 (C_5), 123.0 (C_7 or C_8), 117.2 (C_{4a}), 76.8 (C_2), 74.7 (OCH_2), 52.4 ($CO_2\mathit{C}H_3$), 30.5 (C_3), 25.5 (C_2-$\mathit{C}H_3$), 20.9 (C_4), 12.9 (C_7-$\mathit{C}H_3$), 12.0 (C_8-$\mathit{C}H_3$), 11.9 (C_5-$\mathit{C}H_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{22}H_{26}NaO_4$ $[M+Na]^+$ 377.1723, found 277.1723; m.p = 100-101 °C; $[\alpha]_D^{25}$ -43.9 (*c* 5, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[140]

(*S*)-(6-(Benzyloxy)-2,5,7,8-tetramethylchroman-2-yl)methanol 390

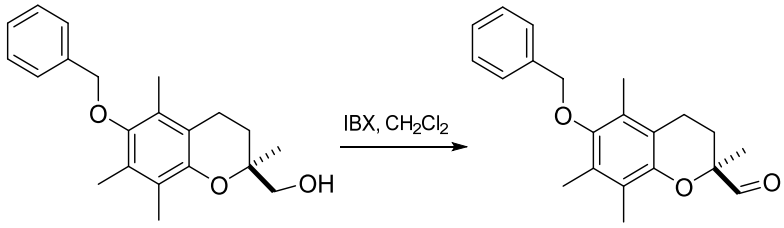


389 390

The compound was prepared according to a literature procedure.[140] To a stirred suspension of $LiAlH_4$ (80.0 mg, 2.03 mmol) in dry THF (6 mL) was added dropwise methyl (*S*)-6-(benzyloxy)-2,5,7,8-tetramethylchromane-2-carboxylate **389** (0.240 g, 0.678 mmol), under nitrogen and at 0 °C. The solution was stirred at 0 °C for one hour then at room temperature for a further two hours. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl (aq.), then filtered through celite. The filtrate was concentrated *in vacuo*, the residue was taken up in EtOAc and washed with brine and water. The organic fractions were dried over Na_2SO_4 and solvent was removed *in vacuo*. The crude residue was purified by column chromatography (3:1 petroleum ether/EtOAc) to yield product as a white solid (0.183 g, 83%). ν (cm^{-1}); 3403 (br, O-H stretch), 1254, 1085 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53-7.30 (5H, m, Ph-H), 4.70 (2H, s, OCH_2), 3.66 (1H, d, *J* 11.5, C*H*HOH), 3.60 (1H, d, *J* 11.5, CH*H*OH), 2.72-2.58 (2H, m, $ArCH_2$), 2.27 (3H, s, C_7-CH_3), 2.18 (3H, s, C_5-CH_3), 2.11 (3H, s, C_8-CH_3), 2.02 (1H, ddd, *J* 13.5, 10, 7, $ArCH_2CHH$), 1.74 (1H, ddd, *J* 13.5, 6, 4.5, $ArCH_2CHH$), 1.24 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.7 (C_6),

147.3 (C_{8a}), 137.9 (Ph-C), 128.5 (Ph-C), 128.3 (C_7 or C_8), 127.9, 127.8 (Ph-C), 126.3 (C_5), 123.0 (C_7 or C_8) 117.6 (C_{4a}), 75.4 (C_2), 74.8 (Ph*C*H_2O), 69.4 (*C*H_2OH), 27.7 (C_3), 20.6 (C_2-*C*H_3), 20.2 (C_4), 12.9 (C_7-*C*H_3), 12.1 (C_5-*C*H_3), 11.9 (C_8-*C*H_3); HRMS (ESI) *m/z*: calcd. for $C_{21}H_{26}NaO_3$ $[M+Na]^+$ 349.1774, found 349.1780; m.p = 68-69 °C; $[\alpha]_D^{25}$ -0.8 (*c* 0.6, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[140]

(*S*)-6-(Benzyloxy)-2,5,7,8-tetramethylchromane-2-carbaldehyde 35

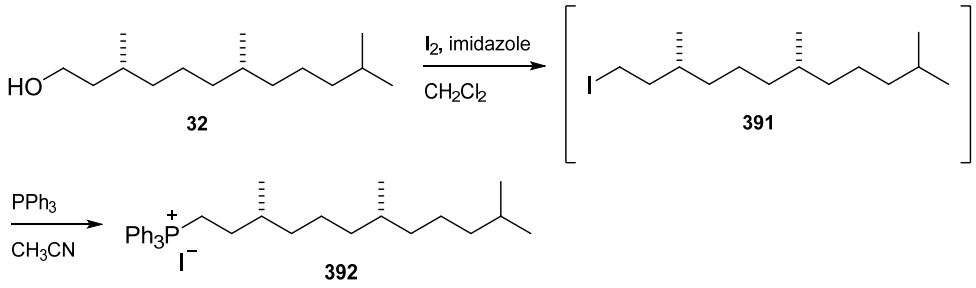


390 **35**

To a solution of IBX (90.0 mg, 0.323 mmol) in DMSO (4 mL) was added a solution of (*S*)-(6-(benzyloxy)-2,5,7,8-tetramethylchroman-2-yl)methanol **390** (70.0 mg, 0.215 mmol) in dry CH_2Cl_2 (2 mL) and the solution was stirred at room temperature overnight. The mixture was filtered through celite with EtOAc and the filtrate was washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as an off-white solid (50 mg, 72%). ν (cm^{-1}); 1737 (C=O stretch), 1253, 1088 (C-O stretch), 698 (Ar-H bend); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (1H, d, *J* 1, CHO), 7.54-7.31 (5H, m, Ph-H), 4.70 (2H, s, OCH_2), 2.62 (1H, dt, *J* 17, 6, ArC*H*H), 2.54 (1H, ddd, *J* 17, 9, 7, ArCH*H*), 2.29 (1H, ddd, *J* 13.5, 6.5, 5, $ArCH_2$C*H*H), 2.25 (3H, s, C_7-CH_3), 2.21 (3H, s, C_8-CH_3), 2.14 (3H, s, C_5-CH_3), 1.84 (1H, dddd, *J* 16, 13.5, 6.5, 1, $ArCH_2$CH*H*), 1.42 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6 (CHO), 149.3 (C_6), 147.6 (C_{8a}), 137.9 (Ph-C), 128.8 (C_7 or C_8), 128.6, 128.0, 127.0 (5 x Ph-C), 126.5 (C_5), 123.3 (C_7 or C_8), 117.9 (C_{4a}), 80.6 (C_2),

74.9 (OCH_2), 27.9 (C_3), 21.7 (C_2-CH_3), 20.4 (C_4), 13.0, 12.12, 12.07 (Ar-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{21}H_{24}NaO_3$ $[M+Na]^+$ 347.1618, found 347.1615; m.p = 54-56 °C; $[\alpha]_D^{25}$ +7.6 (*c* 0.36, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[171, 196]

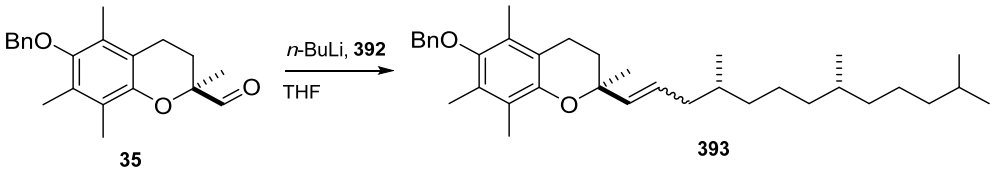
Triphenyl((3*R*,7*R*)-3,7,11-trimethyldodecyl)phosphonium iodide 392



To a solution of (3*R*,7*R*)-hexahydrofarnesol **32** (1.14 g, 5.00 mmol) in dry CH_2Cl_2 (25 mL) was added PPh_3 (1.57 g, 6.00 mmol), imidazole (0.409 g, 6.00 mmol) and I_2 (1.52 g, 6.00 mmol). The mixture was stirred at room temperature for one hour, then the solvent was removed *in vacuo*. The residue was passed through a short plug of silica eluting with pentane, to yield product as a colourless oil (1.40 g, 83%), which was used immediately in the next step. Iodide **391 (**1.40 g, 4.13 mmol) was dissolved in CH_3CN (15 mL), PPh_3 (1.08 g, 4.13 mmol) was added and the solution was stirred at 80 °C for 48 hours. The solvent was removed *in vacuo* to yield the phosphonium salt **392** as a viscous oil (1.94 g, 78%) which solidified on standing. ν (cm^{-1}); 2923 (C-H stretch), 1436 (P-Ph stretch), 739 and 689 (Ar-H bend monosubsituted benzene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87-7.70 (15H, m, Ph-H), 3.71-3.60 (2H, m, C*H*$_2$$PPh_3$), 1.85-1.74 (1H, m, C*H*$CH_2CH_2PPh_3$), 1.66-1.54 (1H, m, C*H*HCH_2PPh_3), 1.53-1.47 (1H, m, C*H*CH_3), 1.46-1.37 (1H, m, CH*H*CH_2PPh_3), 1.34-0.95 (13H, m, CH_2 and CH), 0.99 (3H, d, *J* 7.5, C*H*$_3$$CHCH_2CH_2PPh_3$), 0.85 (6H, d, *J* 6.5, C*H*$_3$CH), 0.79 (3H, d, *J* 6.5, C*H*$_3$CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.2 (Ph-C), 133.9 (d, *J* 10, Ph-C), 130.7 (d, *J* 12.5, Ph-C), 130.5 (d, *J* 471.5, Ph-C), 39.5, 37.4, 37.3, 36.8 (CH_2), 33.7 (d,

J 13, *C*HCH$_2$CH$_2$PPh$_3$), 32.9 (CH$_3$*C*H), 29.5 (d, *J* 4, *C*H$_2$CH$_2$PPh$_3$), 28.1 (CH$_3$*C*H), 24.9, 24.3 (CH$_2$), 22.8, 22.9 (*C*H$_3$CH), 21.4 (d, *J* 50.5, CH$_2$PPh$_3$), 19.8 (*C*H$_3$CH), 19.5, (*C*H$_3$CHCH$_2$CH$_2$PPh$_3$); HRMS (ESI) *m/z*: calcd. for $C_{33}H_{46}P$ $[M]^+$ 473.3332, found 473.3334; m.p = 78-79 °C; $[\alpha]_D^{25}$ -3.7 (*c* 0.27, $CHCl_3$). This compound was previously reported without spectroscopic data.[440]

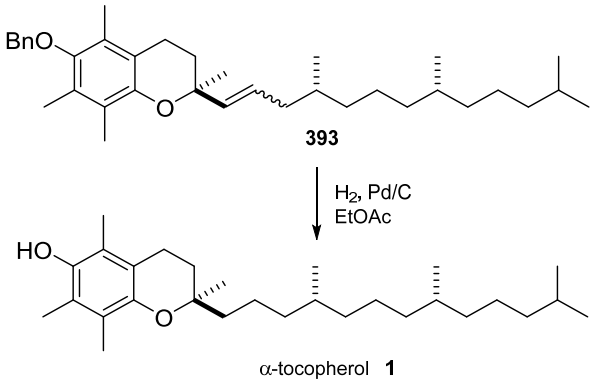
(2*S*,4'*R*,8'*R*)-6-(Benzyloxy)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridec-1'-en-1'-yl)chromane 393



To a solution of triphenyl((3*R*,7*R*)-3,7,11-trimethyldodecyl)phosphonium iodide **392** (0.430 g, 0.717 mmol) in dry THF (3.8 mL) was added *n*-BuLi (2.23 M, 0.290 mL, 0.652 mmol) at 0 °C under nitrogen. After stirring for one hour at this temperature a solution of (*S*)-6-(benzyloxy)-2,5,7,8-tetramethylchromane-2-carbaldehyde **35** (0.106 g, 0.327 mmol) in THF (1.2 mL) was added dropwise and the solution was stirred at room temperature for two hours. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with Et_2O, the combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. To remove triphenylphosphine (present due to incomplete conversion in the synthesis of phosphonium salt **392**) the residue was dissolved in THF (2 mL) and MeI (0.100 mL, 1.60 mmol) was added. This mixture was stirred at room temperature until the triphenylphosphine was consumed as monitored by TLC. The solids were filtered off and the crude residue was purified by column chromatography (1:39 Et_2O/petroleum ether) to yield product as a colourless oil (0.142 g, 73%), as a mixture of *cis*/*trans* isomers. ν (cm^{-1}); 2925 (C-H stretch), 1253,1088 (C-O stretch), 732, 696 (Ar-H bend);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54-7.30 (5H, m, Ph-H), 5.87 (1H, dd, *J* 13.5, 11, *trans*-C*H*=CH), 5.47-5.29 (2H, m, *cis*-C*H*=C*H*), 5.03 (1H, dd, *J* 11, 1.5, *trans*-CH=C*H*), 4.69 (2H, s, OCH_2), 2.68-2.53 (2H, m, $ArCH_2$), 2.26-2.06 (2H, m, CH=CHCH_2), 2.21 (3H, s, Ar-CH_3), 2.15 (6H, s, Ar-CH_3), 2.02 (1H, dt, *J* 13.5, 5.5, $ArCH_2$C*H*H), 1.77 (1H, ddd, *J* 16, 8.5, 7, $ArCH_2$CH*H*), 1.54-1.46 (1H, m, H_4'), 1.49 (3H, s, C_2-CH_3), 1.38-0.97 (14H, m, $(CH_2)_3CH(CH_2)_3CH$), 0.88-0.80 (12H, m, CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.4, 148.2 (C_6 and C_{8a}), 138.2 (Ph-C), 134.0 (*C*H=CH), 131.7 (CH=*C*H), 128.6 (2 x Ph-C), 128.1 (C_7 or C_8), 127.81, 127.88 (Ph-C), 126.1 (C_5), 122.9 (C_7 or C_8), 118.2 (C_{4a}), 76.0 (C_2), 74.8 (OCH_2), 39.5, 37.5, 37.4, 37.3, (CH_2), 35.2 (CH=CH*C*H_2), 33.7 (CH), 33.4, (C_3), 33.0 (CH), 28.1 (CH), 27.3 (C_2-*C*H_3), 25.0, 24.8 (CH_2), 22.9, 22.8 (CH*C*H_3), 21.2 (C_4), 19.9, 19.8 (CH*C*H_3), 13.0 (Ar-CH_3), 12.3 (Ar-CH_3), 12.2 (Ar-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{36}H_{54}NaO_2$ $[M+Na]^+$ 541.4016, found 541.4019; $[\alpha]_D^{20}$ -27.5 (*c* 0.04, $CHCl_3$). This compound was previously reported with incomplete ^{1}H and ^{13}C NMR data.[394]

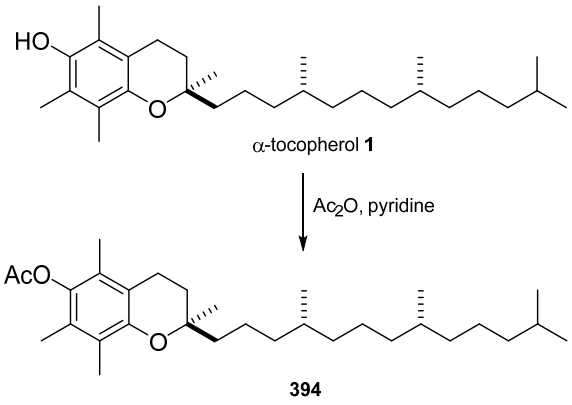
α-Tocopherol 1



To a solution of (2*S*,4'*R*,8'*R*)-6-(benzyloxy)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridec-1'-en-1'-yl)chromane **393** (98.0 mg, 0.189 mmol) in EtOAc (5 mL) was added 10% Pd/C (40.0 mg, 0.0378 mmol) and the mixture was stirred at room temperature under an atmosphere of hydrogen for one hour. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give a crude product which

was purified by column chromatography (95:5 petroleum ether/EtOAc), to yield α-tocopherol **1** as a colourless oil (78 mg, 96%). ν (cm^{-1}); 3407 (br, O-H stretch), 2926 (C-H stretch), 1212, 1086 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.16 (1H, s, OH), 2.60 (2H, t, *J* 7, $ArCH_2$), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, Ar-CH_3), 1.86-1.71 (2H, m, $ArCH_2CH_2$), 1.61-0.99 (21H, m, $(CH_2)_3CH(CH_2)_3CH(CH_2)_3CH$)), 1.23 (3H, s, C_2-CH_3), 0.93-0.79 (12H, m, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.7 (C_{4a}), 144.7 (C_{8a}), 122.8 (C_7), 121.1 (C_8), 118.6 (C_6), 117.5 (C_5), 74.7 (C_2), 40.0 (C_1'), 39.5 (C_{11}'), 37.62 (C_3'), 37.60 (C_9'), 37.58 (C_5'), 37.4 (C_7'), 33.0 (C_8'), 32.9 (C_4'), 31.7 (C_3), 28.1 (C_{12}'), 25.0 (C_{10}'), 24.6 (C_6'), 24.0 (C_2-CH_3), 22.9, 22.8 (C_{12}'-CH_3), 21.2 (C_2'), 20.9 (C_4), 19.9 (C_8'-CH_3), 19.8 (C_4'-CH_3), 12.4 (C_7-CH_3), 11.9 (C_8-CH_3), 11.4 (C_5-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{29}H_{49}O_2$ $[M-H]^-$ 429.3738, found 429.3735; $[\alpha]_D^{20}$ +1.0 (*c* 0.2, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[171]

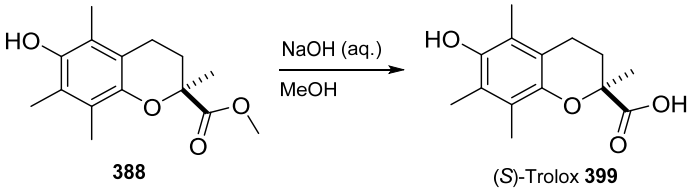
α-Tocopheryl acetate 394



α-Tocopherol **1** (78 mg, 0.18 mmol) was stirred in a solution of Ac_2O (0.40 mL) and pyridine (1 mL) at room temperature for 18 hours. After this time the volatiles were removed under high vacuum and the residue was purified by column chromatography (9:1 petroleum ether/Et_2O), to yield product as a colourless oil (75 mg, 90%). ν (cm^{-1}); 2925 (C-H stretch), 1757 (C=O stretch), 1207 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500

MHz) δ 2.59 (2H, t, *J* 7, $ArCH_2$), 2.33 (3H, s, $OCOCH_3$), 2.09 (3H, s, C_5-CH_3), 2.02 (3H, s, C_8-CH_3), 1.98 (3H, s, C_7-CH_3), 1.85-1.70 (2H, m, $ArCH_2CH_2$), 1.60-1.00 (21H, m, $(CH_2)_3CH(CH_2)_3CH(CH_2)_3CH$)), 1.23 ($C_2$-$CH_3$), 0.89-0.80 (12H, m, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0 ($OCOCH_3$), 149.6 (C_{4a}), 140.6 (C_{8a}), 126.8 (C_7 or C_8), 125.0 (C_6), 123.2 (C_7 or C_8), 117.5 (C_5), 75.1 (C_2), 39.5, 37.6, 37.8, 37.56, 37.54, 37.4 (CH_2), 32.9, 32.8 (CH), 31.1 (C_3), 28.1 (CH), 25.0, 24.6 (CH_2), 24.4 (C_2-CH_3), 22.9, 22.8 ($CHCH_3$), 21.2 (CH_2), 20.74 (C_4), 20.72 ($OCOCH_3$), 19.9, 19.8 ($CHCH_3$), 13.1, 12.2, 12.0 (Ar-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{31}H_{52}NaO_3$ $[M+Na]^+$ 495.3809, found 495. 3811; $[\alpha]_D^{25}$ +3.7 (*c* 0.25, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[171]

(*S*)-Trolox 399

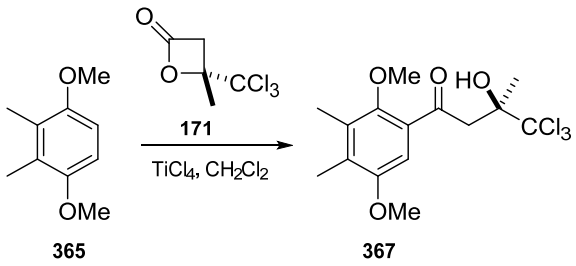


388 (*S*)-Trolox **399**

To a solution of methyl (*S*)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylate **388** (0.100 g, 0.400 mmol) in MeOH (3 mL) was added 2M NaOH (aq.) (2 mL, 4.00 mmol) and the solution was stirred at 80 °C for 16 hours. After cooling to room temperature, the pH of the solution was adjusted to ≤ 2 using concentrated HCl (aq.). The product was extracted with EtOAc, the combined organic fractions were washed with water, dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield product as a brown crystalline solid. ν (cm^{-1}); 3442 (O-H stretch), 2930 (C-H stretch), 1715 (acid C=O stretch), 1648 (ketone C=O stretch), 1085 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.68 (1H, dt, *J* 17, 6, $ArCHH$), 2.60 (1H, ddd, *J* 17, 9.5, 6.5, $ArCHH$), 2.37 (1H, dt, *J* 13.5, 6, $ArCH_2CHH$), 2.17 (6H, s, Ar-CH_3), 2.09 (3H, s, Ar-CH_3), 1.98-1.89 (1H, m, $ArCH_2CHH$), 1.61 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2

(CO_2), 146.0 (C_6), 144.6 (C_{8a}), 122.6, 121.6, 118.8, 117.3 (Ar-C), 77.2 (C_2), 30.1 (C_3), 24.5 (C_2-CH_3), 20.7 (C_4), 12.3, 12.0, 11.4 (Ar-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{14}H_{18}NaO_4$ $[M+Na]^+$ 273.1097, found 273.1097; m.p = 157-159 °C; $[\alpha]_D^{25}$ -50 (*c* 1.02, MeOH). Spectroscopic data are consistent with that previously reported in the literature.[420]

(*R*)-4,4,4-Trichloro-1-(2',5'-dimethoxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one 367

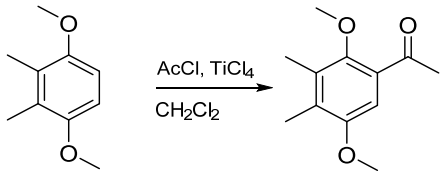


365 **367**

A solution of 1,4-dimethoxy-2,3-dimethylbenzene (16.8 g, 101 mmol) **365** in CH_2Cl_2 (60 mL) was cooled to 0 °C and $TiCl_4$ (3.33 mL, 30.3 mmol) was added dropwise under nitrogen. After stirring for five minutes, (*R*)-(+)-4-methyl-4-(trichloromethyl)-2-oxetanone **171** (2.05 g, 10.1 mmol) dissolved in minimum CH_2Cl_2 was added dropwise and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with water, brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (95:5 petroleum ether/EtOAc to 8:2) to yield product as a yellow oil (3.14 g, 84%, ≥ 98% *e.e.*). ν (cm^{-1}); 3442 (br, O-H stretch), 1655 (C=O stretch), 1232, 1101 (C-O stretch), 792 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (1H, s, Ar-H), 5.53 (1H, s, OH), 3.84 (1H, d, *J* 16.5, C*H*HCO), 3.83 (3H, s, C_2'-OCH_3), 3.73 (1H, d, *J* 16.5, CH*H*CO), 3.72 (3H, s, C_5'-OCH_3), 2.24 (3H, s, C_3'-CH_3), 2.19 (3H, s, C_4'-CH_3), 1.70 (3H, s, C_3-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8 (CO), 154.0 (C_5'), 152.2 (C_2'),

133.7 (C_4'), 132.3 (C_3'), 129.4 (C_1'), 107.8 (C_6' and CCl_3), 92.5 (C_3), 62.5 (C_2'-O*C*H$_3$), 55.8 (C_5'-O*C*H$_3$), 46.1 (CH_2), 23.5 (C_3-*C*H$_3$), 12.79 (2 x Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{15}H_{19}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 391.0241, found 391.0239; $[\alpha]_D{}^{25}$ +15.6 (*c* 1.8, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel AD-H column, 2-propanol : hexane = 4 : 96, 1 mL/min, 227 nm, (*S*) isomer 18.55 min, (*R*) isomer 19.88 min).

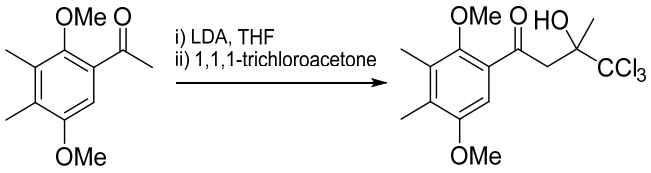
1-(2',5'-Dimethoxy-3',4'-dimethylphenyl)ethan-1-one



365

A solution of 1,4-dimethoxy-2,3-dimethyl benzene **365** (12.9 g, 77.7 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and $TiCl_4$ (2.56 mL, 23.3 mmol) was added under nitrogen. After stirring for 10 minutes, acetyl chloride (0.550 mL, 7.77 mmol) was added dropwise and the solution was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (97.5:2.5 petroleum ether/EtOAc to 8:2) to yield product as a yellow oil (2.15 g, 66%). ν (cm^{-1}); 1654 (C=O stretch), 1100 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (1H, s, Ar-H), 3.82 (3H, s, C_2'-OCH_3), 3.69 (3H, s, C_5'-OCH_3), 2.66 (3H, s, COCH_3), 2.24 (3H, s, C_4'-CH_3), 2.18 (3H, s, C_3'-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.6 (CO), 153.8 (C_2'), 152.4 (C_5'), 132.3 (C_1'), 132.0 (C_3' or C_4'), 130.1 (C_3' or C_4'), 108.0 (C_6'), 62.4 (C_5'-O*C*H$_3$), 55.9 (C_2'-O*C*H$_3$), 30.8 (CO*C*H$_3$), 12.8 (C_3'-*C*H$_3$ and C_4'-*C*H$_3$); LRMS (ESI) *m*/*z*: calcd. for $C_{12}H_{16}NaO_3$ $[M+Na]^+$ 231.1, found 231.1. Spectroscopic data are consistent with that previously reported.[441]

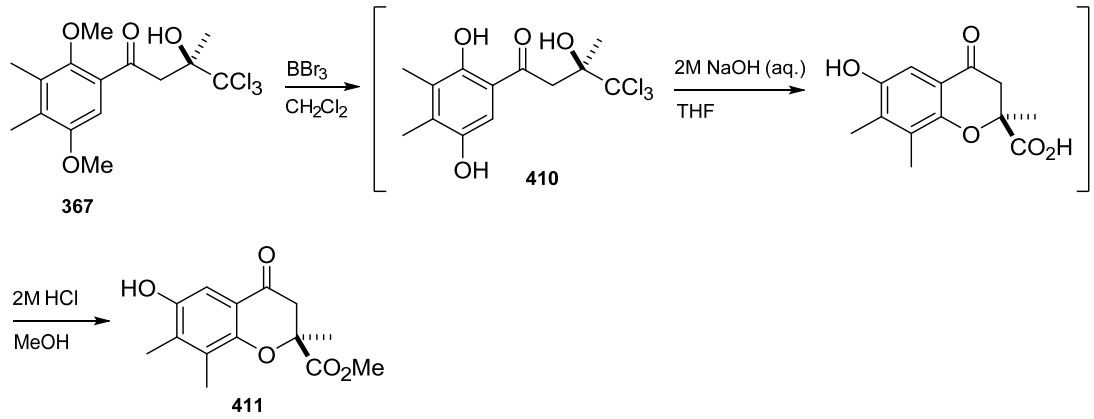
4,4,4-Trichloro-1-(2',5'-dimethoxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-367



(±)-**367**

A solution of diisopropylamine (1.74 mL, 12.4 mmol) in dry Et_2O (50 mL) was cooled to -78 °C and *n*-BuLi (2.5 M, 4.52 mL, 11.3 mmol) was added dropwise. After stirring for 30 minutes at this temperature, 1-(2',5'-dimethoxy-3',4'-dimethylphenyl)ethan-1-one (2.15 g, 10.3 mmol) was added dropwise over 20 minutes. After stirring for one hour 1,1,1-trichloroacetone (1.75 mL, 15.5 mmol) was added slowly over 20 minutes and the mixture was stirred at -78 °C for a further three hours, before warming to room temperature and stirring overnight. The reaction was quenched with saturated NH_4Cl (aq.) (20 mL), extracted with Et_2O and the organic fractions were washed with water and brine. The solvent was removed *in vacuo* and the residue was purified by column chromatography yield product as a yellow oil (1.97 g, 52%) after column chromatography (100% CH_2Cl_2) . ν (cm^{-1}); 3442 (br, O-H stretch), 1654 (C=O stretch), 1100 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (1H, s, Ar-H), 5.53 (1H, s, OH), 3.85 (1H, d, *J* 17, C*H*HCO), 3.83 (3H, s, C_2'-OCH_3), 3.73 (1H, d, *J* 16.5, CH*H*CO), 3.72 (3H, s, C_5'-OCH_3), 2.24 (3H, s, C_3'-CH_3), 2.19 (3H, s, C_4'-CH_3), 1.70 (3H, s, C_3-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.9 (CO), 154.2 (C_5'), 152.3 (C_2'), 133.8 (C_4'), 132.4 (C_3'), 129.6 (C_1'), 108.0 (CCl_3), 107.9 (C_6'), 82.6 (C_3), 62.7 (C_2'-O*C*H_3), 55.9 (C_5'-O*C*H_3), 46.3 (CH_2), 23.7 (C_3-*C*H_3), 12.9 (2 x Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{15}H_{19}{}^{35}Cl_3NaO_4$ $[M+Na]^+$ 391.0241, found 391.0238.

Methyl (*S*)-6-hydroxy-2,7,8-trimethyl-4-oxochromane-2-carboxylate 411

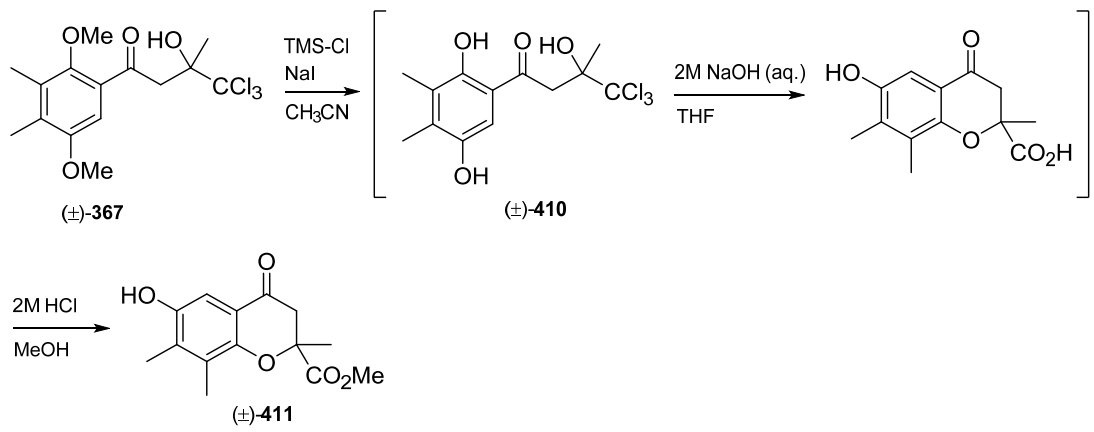


To a solution of (*R*)-4,4,4-trichloro-1-(2',5'-dimethoxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one **367** (0.240 g, 0.649 mmol) in dry CH_2Cl_2 (5 mL) was added BBr_3 (0.250 mL, 2.60 mmol) at -78 °C under nitrogen, and the mixture was warmed to room temperature and stirred overnight. After this time the reaction was quenched with water and the solvent was removed under a flow of nitrogen. To obtain the best yields, the crude mixture of hydroquinone **410** was reacted immediately in the next step. To a deoxygenated solution of crude (*R*)-4,4,4-trichloro-1-(2',5'-dihydroxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one **410** in THF (5 mL) was added deoxygenated 2M NaOH (aq.) until the solution reached a pH of ≥ 12 (5 mL, 10.0 mmol), and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield product as a brown crystalline solid which was used in the next step without further purification. A sample of the acid for analysis could be obtained by column chromatography (8:2:0.1 EtOAc/MeOH/AcOH). ν (cm^{-1}); 3392 (br, O-H stretch), 1735 (acid C=O stretch), 1602 (ketone C=O stretch), 1236 and 1085 (C-O stretch); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 6.95 (1H, s, H_5), 2.95 (1H, d, *J* 17, C*H*HCO), 2.88 (1H,

d, *J* 17, CH*H*CO), 2.14 (3H, s, C_8-CH_3), 2.11 (3H, s, C_7-CH_3), 1.61 (3H, s, C_2-CH_3); ^{13}C NMR: ($(CD_3)_2SO$, 125 MHz) δ 191.2 (CO), 174.1 (CO_2), 151.6 (C_6), 149.3 (C_{8a}), 133.1 (C_{4a}), 126.3 (C_7 or C_8), 117.6 (C_7 or C_8), 106.1 (C_5), 80.9 (C_2), 45.2 (CH_2), 24.8 (C_2-*C*H_3), 13.2 (C_7-*C*H_3), 12.3 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{13}H_{13}O_5$ [M-H]$^-$ 249.0768, found 249.0771; m.p = 219-220 °C; $[\alpha]_D^{25}$ -83.3 (*c* 0.012, MeOH).

Crude (*S*)-6-hydroxy-2,7,8-trimethyl-4-oxochromane-2-carboxylic acid was dissolved in 2M methanolic HCl (5 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The crude product was purified using column chromatography (8:2 petroleum ether/EtOAc) to yield the ester as a brown solid (50 mg, 30% from **367**, ≥ 98% *e.e.*) after column chromatography (8:2 petroleum ether/EtOAc). ν (cm^{-1}); 3277 (br, O-H stretch), 1735 (ester C=O stretch), 1680 (ketone C=O stretch), 1204 and 1083 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (1H, s, H_5), 5.80 (1H, s, C_6-OH), 3.65 (3H, s, CO_2CH_3), 3.18 (1H, d, *J* 17, C*H*HCO), 2.83 (1H, d, *J* 17, CH*H*CO), 2.24 (3H, s, C_7-CH_3), 2.23 (3H, s, C_8-CH_3), 1.72 (C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.4 (CO), 172.8 (CO_2), 153.1 (C_6), 148.9 (C_{8a}), 134.7 (C_7), 127.6 (C_8), 117.9 (C_{4a}), 107.5 (C_5), 81.4 (C_2), 53.1 (CO_2*C*H_3), 45.7 (CH_2), 25.4 (C_2-*C*H_3), 13.2 (C_7-*C*H_3), 12.1 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{16}NaO_5$ [M+Na]$^+$ 287.0890, found 287.0891; m.p = 159-160 °C; $[\alpha]_D^{25}$ +45.6 (*c* 0.08, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel AD-H column, 2-propanol : hexane = 6 : 94, 1 mL/min, 231 nm, (*S*) isomer 19.64 min, (*R*) isomer 22.59 min).

Methyl 6-hydroxy-2,7,8-trimethyl-4-oxochromane-2-carboxylate (±)-411

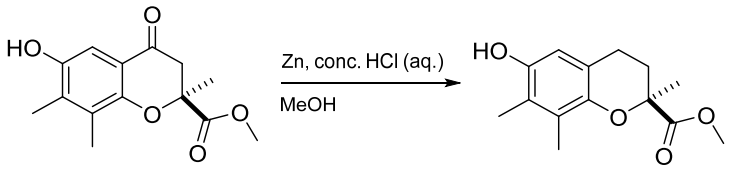


4,4,4-Trichloro-1-(2',5'-dihydroxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**410** was prepared according to a procedure adapted from the literature.[400] To a solution of 4,4,4-trichloro-1-(2',5'-dimethoxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**367** (0.770g, 2.08 mmol) and sodium iodide (2.19 g, 14.6 mmol) in dry CH_3CN (25 mL) was added chlorotrimethylsilane (1.86 mL, 14.6 mmol), slowly with continuous stirring under nitrogen. The reaction mixture was heated to 70 °C for 60 hours, before being quenched with water and extracted with Et_2O. The organic layer was washed with 5% sodium thiosulfate (aq.), brine and dried over Na_2SO_4. The crude hydroquinone (±)-**410** was not isolated and was used in the next step without further purification. To a deoxygenated solution of crude 4,4,4-trichloro-1-(2',5'-dihydroxy-3',4'-dimethylphenyl)-3-hydroxy-3-methylbutan-1-one (±)-**410** in THF (10 mL) was added deoxygenated 2M NaOH (aq.) until the solution reached a pH of ≥ 12 (10 mL, 20.0 mmol), and the mixture was stirred under nitrogen at room temperature overnight. The resulting alkaline solution was washed three times with Et_2O, acidified to pH 2 with 1M HCl (aq.) and extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield product as a brown crystalline solid which was used in the next step without further purification. A pure sample of the acid for analysis

could be obtained by column chromatography (100% EtOAc to 8:2:0.1 EtOAc/MeOH/AcOH). ν (cm^{-1}); 3412 (br, O-H stretch), 1707 (acid C=O stretch), 1671 (ketone C=O stretch), 1204 and 1088 (C-O stretches); ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 9.28 (1H, s, Ar-OH), 6.95 (1H, s, H_5), 2.95 (1H, d, *J* 17, C*H*HCO), 2.91 (1H, d, *J* 17, CH*H*CO), 2.14 (3H, s, C_8-CH_3), 2.11 (3H, s, C_7-CH_3), 1.62 (3H, s, C_2-CH_3); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz) δ 191.0 (CO), 174.0 (CO_2), 152.0 (C_6), 149.9 (C_{8a}), 133.7 (C_{4a}), 126.8 (C_7 or C_8), 118.1 (C_7 or C_8), 106.7 (C_5), 81.3 (C_2), 45.6 (CH_2), 25.2 (C_2-*C*H_3), 13.3 (C_7-*C*H_3), 12.3 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{13}H_{14}NaO_5$ $[M+Na]^+$ 273.0733, found 273.0729; m.p = 263-264 °C.

Crude 6-hydroxy-2,7,8-trimethyl-4-oxochromane-2-carboxylic acid was dissolved in 2M methanolic HCl (5 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was extracted with Et_2O, the combined organic fractions were washed with water and brine and dried over Na_2SO_4. The crude product was purified by column chromatography (8:2 petroleum ether/EtOAc) to yield product as an off-white solid (116 mg, 23% from (±)-**367**). ν (cm^{-1}); 3339 (br, O-H stretch), 1748 (ester C=O stretch), 1666 (ketone C=O stretch), 1198 and 1087 (C-O stretches); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (1H, s, H_5), 4.73 (1H, s, OH), 3.65 (3H, s, CO_2CH_3), 3.17 (1H, d, *J* 17, C*H*HCO), 2.82 (1H, d, *J* 17, CH*H*CO), 2.25 (3H, s, C_7-CH_3), 2.22 (3H, s, C_8-CH_3), 1.72 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.6 (CO), 172.6 (CO_2), 152.6 (C_6), 148.3 (C_{8a}), 134.0 (C_7), 127.4 (C_8), 117.9 (C_{4a}), 107.3 (C_5), 81.3 (C_2), 52.9 (CO_2*C*H_3), 45.6 (CH_2), 25.3 (C_2-*C*H_3), 13.0 (C_7-*C*H_3), 12.0 (C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{16}NaO_5$ $[M+Na]^+$ 287.0890, found 287.0895; m.p = 185-186 °C.

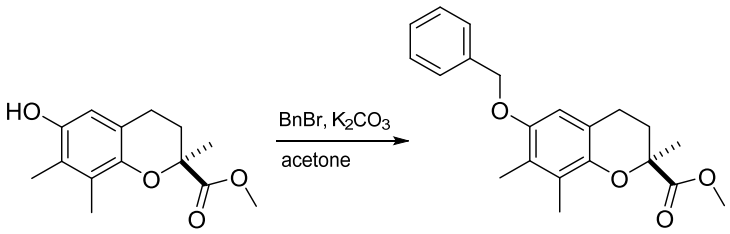
Methyl (*S*)-6-hydroxy-2,7,8-trimethylchromane-2-carboxylate 412



411 412

To a solution of methyl (*S*)-6-hydroxy-2,7,8-trimethyl-4-oxochromane-2-carboxylate **411** (0.550 g, 1.98 mmol) in MeOH (25 mL) was added fine zinc powder (1.36 g, 20.8 mmol) and concentrated HCl (4.30 mL, 52.0 mmol) and stirred at room temperature for five hours. After filtering through celite, the filtrate was concentrated *in vacuo*. The resulting residue was taken up with Et_2O and washed with brine. The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (85:15 petroleum ether/EtOAc) to yield product as a white solid (0.406 g, 78%). ν (cm^{-1}); 3447 (br, O-H stretch), 1729 (C=O stretch), 1190 and 1107 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (1H, s, H_5), 4.34 (1H, s, OH), 3.68 (3H, s, CO_2CH_3), 2.66-2.58 (2H, m, $ArCH_2$), 2.35 (1H, ddd, *J* 13.5, 6, 4.5, $ArCH_2CHH$), 2.18 (3H, s, Ar-CH_3), 2.13 (3H, s, Ar-CH_3), 1.85 (1H, ddd, *J* 17.5, 9.5, 8, $ArCH_2CHH$), 1.60 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6 (CO_2), 147.1 (C_{8a}), 145.7 (C_6), 125.9 (C_7 or C_8), 122.1 (C_{4a}), 118.0 (C_7 or C_8), 112.1 (C_5), 77.9 (C_2), 52.5 (CO_2CH_3), 30.7 (C_3), 25.7 (C_4), 22.8 (C_2-CH_3), 12.1 (C_7-CH_3 or C_8-CH_3), 12.0 (C_7-CH_3 or C_8-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{18}NaO_4$ $[M+Na]^+$ 273.1097, found 273.1102; m.p = 104-105 °C; $[\alpha]_D^{25}$ -81.7 (*c* 0.06, $CHCl_3$).

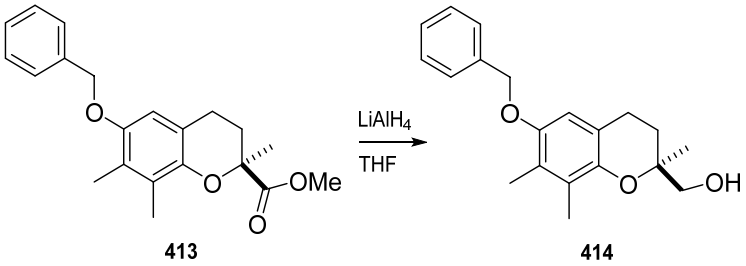
Methyl (*S*)-6-(benzyloxy)-2,7,8-trimethylchromane-2-carboxylate 413



412 **413**

The compound was prepared according to a literature procedure.[140] To a solution of methyl (*S*)-6-hydroxy-2,7,8-trimethylchromane-2-carboxylate **412** (0.400 g, 0.573 mmol) in DMF (5 mL) was added K_2CO_3 (0.330 g, 2.40 mmol) at 0 °C and stirred for 20 minutes. Benzyl bromide (0.285 mL, 2.40 mmol) was then added dropwise and the mixture was stirred at room temperature overnight. The reaction was diluted with water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed thoroughly with water and dried over Na_2SO_4. The solvent was removed *in vacuo* and residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as a white solid (0.340 g, 63%). ν (cm^{-1}); 1727 (C=O stretch), 1206 and 1101 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.41 (2H, m, Ph-H), 7.40-7.35 (2H, m, Ph-H), 7.34-7.29 (1H, m, Ph-H), 6.44 (1H, s, H_5), 5.00 (2H, s, OCH_2), 3.68 (3H, s, CO_2CH_3), 2.73-2.62 (2H, m, $ArCH_2$), 2.38 (1H, ddd, *J* 13.5, 5.5, 4.5, $ArCH_2CHH$), 2.20 (3H, s, C_7-CH_3), 2.19 (3H, s, C_8-CH_3), 1.87 (1H, ddd, *J* 13.5, 10, 7.5, $ArCH_2CHH$), 1.61 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (CO_2), 150.6 (C_{8a}), 145.9 (C_6), 138.0 (Ph-C), 128.4 (Ph-C), 127.6 (Ph-C), 127.2 (Ph-C), 125.9 (C_8), 125.1 (C_{4a}), 117.1 (C_7), 109.9 (C_5), 77.8 (C_2), 70.8 (OCH_2), 52.4 (CO_2CH_3), 30.6 (C_3), 25.5 (C_2-CH_3), 23.0 (C_4), 12.1 (C_7-CH_3 or C_8-CH_3), 12.0 (C_7-CH_3 or C_8-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{21}H_{24}NaO_4$ $[M+Na]^+$ 363.1567, found 363.1570; m.p = 56-57 °C; $[\alpha]_D^{25}$ -31.1 (*c* 0.42, $CHCl_3$).

(*S*)-(6-(Benzyloxy)-2,7,8-trimethylchroman-2-yl)methanol 414

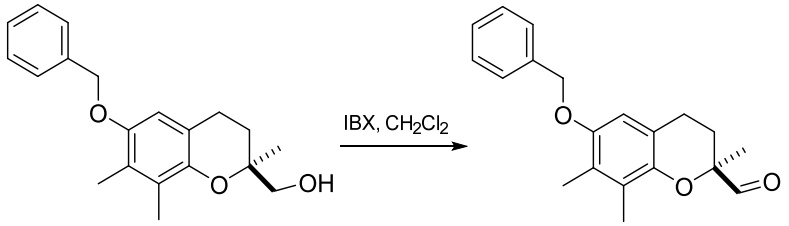


413 414

The compound was prepared according to a literature procedure.[140] To a stirred suspension of $LiAlH_4$ (0.109 g, 2.87 mmol) in dry THF (8 mL) was added dropwise methyl (*S*)-6-(benzyloxy)-2,7,8-trimethylchromane-2-carboxylate **413** (0.325 g, 0.956 mmol), under nitrogen and at 0 °C. The solution was stirred at 0 °C for one hour then at room temperature for a further two hours. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl (aq.), then filtered through celite. The filtrate was concentrated *in vacuo*, the residue was taken up in EtOAc and washed with brine and water. The organic fractions were dried over Na_2SO_4 and solvent was removed *in vacuo*. The resulting white solid was used without further purification (0.250 g, 84%). ν (cm^{-1}); 3458 (br, O-H stretch), 1229 and 1098 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47-7.43 (2H, m, Ph-H), 7.41-7.36 (2H, m, Ph-H), 7.34 (1H, m, Ph-H), 6.52 (1H, s, H_5), 4.98 (2H, s, OCH_2), 3.65 (1H, dd, *J* 11.5, 6.5, C*H*HOH), 3.60 (1H, dd, *J* 11.5, 7, CH*H*OH), 2.81 (1H, ddd, *J* 16.5, 10.5, 6, ArC*H*H), 2.71 (1H, dt, *J* 16.5, 5.5, ArCH*H*), 2.19 (3H, s, C_7-CH_3), 2.13 (3H, s, C_8-CH_3), 2.00 (1H, ddd, *J* 13.5, 10.5, 6, $ArCH_2$C*H*H), 1.90 (1H, t, *J* 6.5, OH), 1.68 (1H, ddd, *J* 13.5, 6.5, 4.5, $ArCH_2$CH*H*), 1.25 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.5 (C_6), 145.5 (C_{8a}), 138.1 (Ph-C), 128.6 (Ph-C), 127.8 (Ph-C), 127.4 (Ph-C), 126.1 (C_{4a}), 125.3 (C_7), 117.7 (C_8), 110.4 (C_5), 76.2 (C_2), 71.1 ($PhCH_2O$), 69.7 (CH_2OH), 28.0 (C_3), 22.4 (C_4), 20.9 (C_2-*C*H_3), 12.2 (C_7-*C*H_3 or C_8-*C*H_3), 12.1 (C_7-*C*H_3 or C_8-*C*H_3); HRMS (ESI) *m*/*z*: calcd.

for $C_{20}H_{24}NaO_3$ $[M+Na]^+$ 335.1618, found 335.1620; m.p = 123-124 °C; $[\alpha]_D^{25}$ +22.5 (*c* 0.14, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[442]

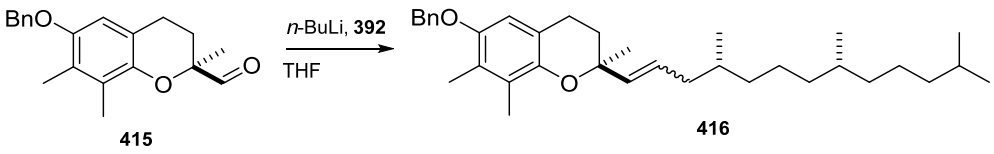
(*S*)-6-(Benzyloxy)-2,7,8-trimethylchromane-2-carbaldehyde 415



414 **415**

To a solution of IBX (0.188 g, 0.673 mmol) in DMSO (4 mL) was added a solution of (*S*)-(6-(benzyloxy)-2,7,8-trimethylchroman-2-yl)methanol **414** (0.140 g, 0.448 mmol) in dry CH_2Cl_2 (2mL) and the solution was stirred at room temperature overnight. The mixture was filtered through celite with EtOAc and the filtrate was washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (95:5 petroleum ether/EtOAc) to yield product as an off-white solid (90 mg, 65%). ν (cm^{-1}); 1739 (C=O stretch), 1102 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (1H, s, CHO), 7.47-7.43 (2H, m, Ph-H), 7.42-7.37 (2H, m, Ph-H), 7.35 (1H, m, Ph-H), 6.47 (1H, s, H_5), 4.98 (2H, s, OCH_2), 2.72-2.66 (2H, m, $ArCH_2$), 2.27-2.19 (1H, m, $ArCH_2CHH$), 2.23 (3H, s, Ar-CH_3), 2.22 (3H, s, Ar-CH_3), 1.86-1.78 (1H, m, $ArCH_2CHH$), 1.41 (3H, s, C_2-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.6 (CHO), 151.0 (C_6), 145.6 (C_{8a}), 137.9 (Ph-C), 128.6 (Ph-C), 127.8 (Ph-C), 127.3 (Ph-C), 126.3 (C_{4a}), 125.5 (C_7), 117.4 (C_8), 110.1 (C_5), 81.1 (C_2), 70.9 (OCH_2), 28.0 (C_3), 22.4 (C_4), 21.9 (C_2-CH_3), 12.2 (C_7-CH_3 and C_8-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{22}NaO_3$ $[M+Na]^+$ 333.1461, found 333.1461; m.p = 95-96 °C; $[\alpha]_D^{25}$ +15 (*c* 0.04, $CHCl_3$).

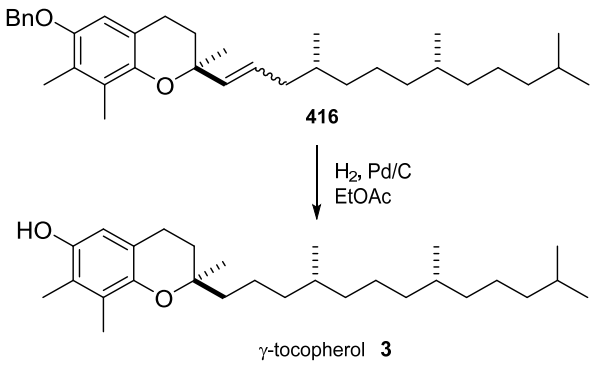
(2*S*,4'*R*,8'*R*)-6-(Benzyloxy)-2,7,8-trimethyl-2-(4',8',12'-trimethyltridec-1-en-1-yl)chromane 416



To a solution of triphenyl((3*R*,7*R*)-3,7,11-trimethyldodecyl)phosphonium iodide **392** (0.612 g, 1.02 mmol) in dry THF (5 mL) was added *n*-BuLi (2.23 M, 0.460 mL, 0.957 mmol) at 0 °C under nitrogen. After stirring for one hour at this temperature a solution of (*S*)-6-(benzyloxy)-2,7,8-trimethylchromane-2-carbaldehyde **415** (90.0 mg, 0.290 mmol) in THF (5 mL) was added dropwise and the solution was stirred at room temperature for two hours. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with Et_2O, the combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. To remove triphenylphosphine (present due to incomplete conversion in the synthesis of phosphonium salt **392**) the residue was dissolved in THF (2 mL) and MeI (50.0 µL, 0.800 mmol) was added. This mixture was stirred at room temperature until the triphenylphosphine was consumed as monitored by TLC. The solids were filtered off and the crude residue was purified by column chromatography (100% petroleum ether to 97.5:2.5 petroleum ether/EtOAc) to yield product as a colourless oil (61 mg, 42%), as a mixture of *cis*/*trans* isomers. ν (cm^{-1}); 2924 (C-H stretch), 1231 and 1098 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49-7.28 (5H, m, Ph-H), 6.49 (1H, s, H_5), 5.85 (1H, dd, *J* 17.5, 11, *trans* C*H*=CH), 5.53-5.29 (2H, m, CH=CH), 4.96 (2H, s, OCH_2), 2.79 (1H, ddd, *J* 16.5, 10, 6, ArC*H*H), 2.63 (1H, dt, *J* 16, 5, ArCH*H*), 2.67-2.14 (1H, m, CH=CHC*H*H), 2.18, (3H, s, Ar-CH_3), 2.17 (3H, s, Ar-CH_3), 2.01 (1H, ddd, *J* 14.5, 5.5, 4, CH=CHCH*H*), 1.96 (1H, ddd, *J* 13.5, 5.5, 5, $ArCH_2$C*H*H), 1.74 (1H, ddd, *J* 16, 10.5, 5.5, $ArCH_2$CH*H*), 1.56-1.46 (1H, m, H_4'), 1.49 (3H, s, C_2-CH_3),

1.42-0.96 (14H, m, $(CH_2)_3CH(CH_2)_3CH$), 0.88-0.80 (12H, m, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.2 (C_6), 146.2 (C_{8a}), 138.2 (Ph-C), 134.1 (*C*H=CH), 131.7 (CH=*C*H), 128.5, 127.7, 127.4 (5 x Ph-C), 125.9 (C_{4a}), 124.9 (C_7), 118.0 (C_8), 110.2 (C_5), 76.6 (C_2), 71.0 (OCH_2), 39.5, 37.5, 37.41, 37.36, (CH_2), 35.1 (CH=CH*C*H_2), 33.7 (CH), 33.4 (C_3), 32.9 (CH), 27.8 (CH), 27.4 (C_2-*C*H_3), 24.9, 24.7, (CH_2), 23.1 (C_4), 22.9, 22.8, 19.9, 19.8, (CH*C*H_3) 12.3 (Ar-CH_3), 12.2 (Ar-CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{35}H_{52}NaO_2$ $[M+Na]^+$ 527.3860, found 527.3853; $[\alpha]_D^{25}$ -14.1 (*c* 0.32, $CHCl_3$).

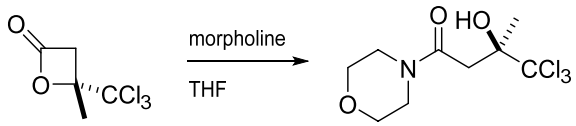
γ-Tocopherol 3



To a solution of (2*S*,4'*R*,8'*R*)-6-(benzyloxy)-2,7,8-trimethyl-2-(4',8',12'-trimethyltridec-1'-en-1'-yl)chromane **416** (20.0 mg, 0.0397 mmol) in EtOAc (3 mL) was added 10% Pd/C (8.00 mg, 7.94 µmol) and the mixture was stirred at room temperature under an atmosphere of hydrogen for one hour. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to yield product as a brown oil (15 mg, 91%). ν (cm^{-1}); 3398 (br, O-H stretch), 2924 (C-H stretch), 1223, 1080 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.37 (1H, s, H_5), 4.23 (1H, s, OH), 2.73-2.61 (2H, m, $ArCH_2$), 2.14 (3H, s, Ar-CH_3), 2.11 (3H, s, Ar-CH_3), 1.82-1.67 (2H, m, $ArCH_2CH_2$), 1.63-1.00 (21H, m, $(CH_2)_3CH(CH_2)_3CH(CH_2)_3CH$), 1.24 (3H, s, C_2-CH_3), 0.90-0.81 (12H, m, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.3 (C_6), 145.9 (C_{8a}), 125.9 (C_8), 121.7 (C_7), 118.5 (C_{4a}), 112.3 (C_5), 75.6 (C_2), 40.2 (C_1'), 39.5 (C_{11}'),

37.61 (C_3'), 37.60 (C_9'), 37.56 (C_5'), 37.4 (C_7'), 32.9 (C_8'), 32.8 (C_4'), 31.5 (C_3), 28.1 (C_{12}'), 25.0 (C_{10}'), 24.6 (C_6'), 24.2 (C_2-*C*H_3), 22.8, 22.9 (C_{12}'-*C*H_3), 22.5 (C_4), 21.2 (C_2'), 19.9 (C_4'-*C*H_3), 19.8 (C_8'-*C*H_3), 12.1 (Ar-CH_3), 12.0 (Ar-CH_3); HRMS (ESI) *m/z*: calcd. for $C_{28}H_{48}NaO_2$ $[M+Na]^+$ 439.3547, found 439.3544; $[\alpha]_D^{20}$ +2.5 (*c* 0.08, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[415]

(*R*)-4,4,4-Trichloro-3-hydroxy-3-methyl-1-morpholinobutan-1-one 428

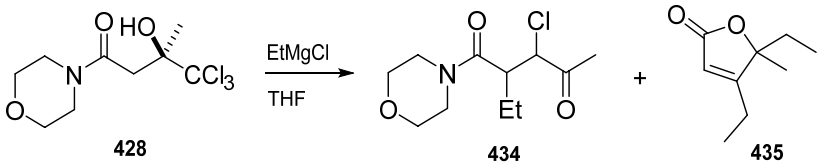


171 **428**

To a solution of (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one **171** (0.230 g, 1.13 mmol) in THF (2 mL) was added morpholine (0.200 mL, 2.26 mmol) and the solution was heated to 70 °C for 25 minutes in a microwave reactor. After this time the solution was washed with pH 2 buffer and the combined aqueous fractions were extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield product as a white solid (0.304 g, 93%). ν (cm^{-1}); 3191 (br, O-H stretch), 1601 (C=O stretch), 1115 (C-O stretch), 801 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.50 (1H, s, OH), 3.77-3.51 (8H, m, CH_2), 3.14 (1H, d, *J* 15.5, C*H*HCO), 2.78 (1H, d, *J* 15.5, CH*H*CO), 1.70 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4 (CO), 107.9 (CCl_3), 82.1 (C(OH)), 66.8 (CH_2), 66.6 (CH_2), 46.6 (CH_2), 42.3 (CH_2), 36.0 (*C*H_2CO), 24.5 (CH_3); HRMS (ESI) *m/z*: calcd. for $C_9H_{14}{}^{35}Cl_3NNaO_3$ $[M+Na]^+$ 311.9931, found 311.9937; m.p = 120-121 °C; $[\alpha]_D^{20}$ +30.0 (*c* 0.76, $CHCl_3$).

3-Chloro-2-ethyl-1-morpholinopentane-1,4-dione 434

4,5-Diethyl-5-methylfuran-2(5H)-one 435

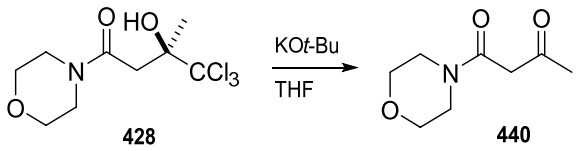


The compounds were isolated as side products in the following reaction. To a solution of (*R*)-4,4,4-trichloro-3-hydroxy-3-methyl-1-morpholinobutan-1-one **428** (0.345 g, 1.19 mmol) in dry THF (5 mL) was added ethylmagnesium bromide (1.19 mL, 2M in THF, 2.38 mmol) at 0 °C, under nitrogen. The solution was warmed to reflux temperature and stirred for 14 hours. The reaction was quenched with 10% AcOH (aq.), extracted with Et_2O and washed with water and brine. The combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography (3:1 petroleum ether/EtOAc) isolated the side product **434** as a single diastereoisomer (5 mg, 1.7%) ν (cm^{-1}); 1725 (ketone C=O stretch), 1628 (amide C=O stretch), 1114 (C-O stretch), 777 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.65 (1H, d, *J* 10, CHCl), 3.85-3.78 (1H, m, CH_2), 3.74-3.62 (6H, m, CH_2), 3.57-3.45 (1H, m, CH_2), 3.17 (1H, ddd, *J* 11.5, 7.5, 4, C*H*CH_2), 2.34 (3H, s, $COCH_3$), 1.90-1.76 (2H, m, C*H*$_2$$CH_3$), 0.94 (3H, t, *J* 7.5, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1 (*C*OCH_3), 171.9 (CON), 67.1, 66.8 (CH_2), 61.8 (CHCl), 46.8 (CH_2), 44.3 (*C*HCH_2), 42.3 (CH_2), 28.0 (CO*C*H_3), 22.6 (*C*$H_2$$CH_3$), 10.2 ($CH_2$*C*$H_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{11}H_{18}{}^{35}ClNNaO_3$ $[M+Na]^+$ 270.0867, found 270.0868.

Lactone **435** was isolated from the same mixture (7 mg, 3.8%) as a colourless oil. Only ^{1}H and ^{13} NMR data were obtained for this compound. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77-5.74 (1H, m, COCH), 2.30-2.12 (2H, m, C_5-CH_2), 1.89 (1H, quin, *J* 7.5, C_4-C*H*H), 1.65 (1H, quin, *J* 7.5, C_4-CH*H*), 1.42 (3H, s, C_5-CH_3), 1.23 (3H, t, *J* 7.5,

CH_2CH_3), 0.78 (3H, t, *J* 7.5, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8 (C_3), 172.7 (CO), 114.8 (C_2), 89.8 (C_4), 30.3 (C_4-CH_2), 24.0 (C_5-CH_3), 20.5 (C_5-CH_2), 11.1 (CH_2CH_3), 7.5 (CH_2CH_3).

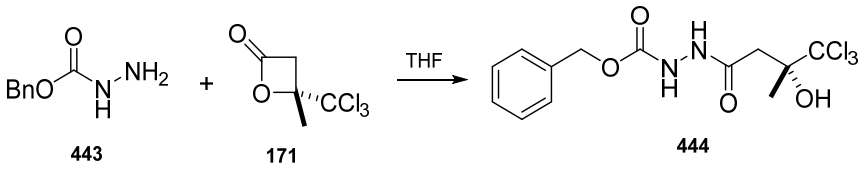
1-Morpholinobutane-1,3-dione 440



428 440

To a solution of (*R*)-4,4,4-trichloro-3-hydroxy-3-methyl-1-morpholinobutan-1-one **428** (0.349 g, 1.21 mmol) in THF (5 mL) was added KO*t*-Bu (0.136 g, 1.21 mmol) at 0 °C, under nitrogen. The mixture was stirred at room temperature for 16 hours, then the reaction was quenched with MeOH and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (100% EtOAc to 95:5 EtOAc/MeOH) to yield product as a colourless amorphous solid (0.108 g, 52%). ν (cm^{-1}); 1717 (ketone C=O stretch), 1630 (amide C=O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ *keto*/*enol* 1:0.18; *keto*: 3.73-3.61 (6H, m, CH_2), 3.56 (2H, s, $COCH_2$), 3.45-3.38 (2H, m, CH_2), 2.28 (3H, s, CH_3); *enol*: 14.6 (1H, s, OH), 5.10 (1H, s, COCH), 3.73-3.61 (8H, m, CH_2), 1.96 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ *keto*: 202.4 (CO), 165.1 (CO), 66.9 (CH_2), 66.7 (CH_2), 50.0 ($COCH_2$), 47.0 (CH_2), 42.3 (CH_2), 30.5 (CH_3); *enol*: 175.3 (C(OH)), 171.0 (CO), 86.3 (COCH), 66.9 (CH_2), 66.7 (CH_2), 47.0 (CH_2), 42.3 (CH_2), 22.2 (CH_3); LRMS (ESI) *m*/*z*: calcd. for $C_8H_{13}NaNO_3$ $[M+Na]^+$ 194.1, found 194.1. Spectroscopic data are consistent with that previously reported.[443]

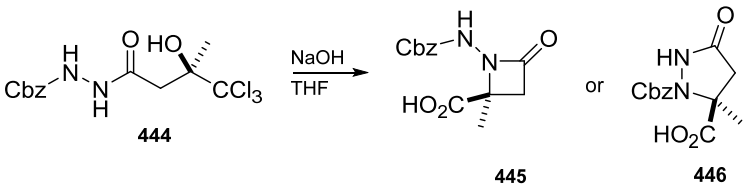
Benzyl-(*R*)-2-(4,4,4-trichloro-3-hydroxy-3-methylbutanoyl)hydrazine-1-carboxylate 444



443 171 444

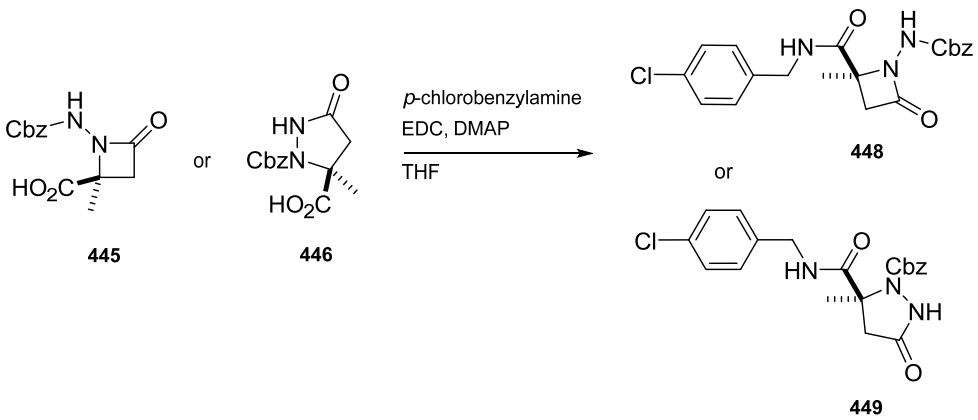
To a solution of (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one **171** (0.398 g, 1.96 mmol) in THF (5 mL) was added benzyl hydrazinecarboxylate (0.440 g, 2.70 mmol) **443** and the solution was heated to 60 °C for 72 hours. After cooling to room temperature, the mixture was diluted with Et_2O and the organic layer was washed with saturated Na_2CO_3 (aq.) and pH 2 buffer. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (6:4 petroleum ether/EtOAc) to yield product as a white solid (657 mg, 92%). ν (cm^{-1}); 3341 (br, O-H stretch), 1730 (C=O stretch), 1678 (C=O stretch), 1216 and 1038 (C-O stretch), 729 and 692 (Ar-H bend); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.81 (1H, s, NH), 9.26 (1H, s, NH), 7.42-7.29 (5H, m, Ph-H), 6.40 (1H, s, OH), 5.09 (1H, s, OCH_2), 2.76 (1H, d, *J* 13, C*H*HCO), 2.65 (1H, d, *J* 13, CH*H*CO), 1.63 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5 (*C*OCH_2), 156.0 (CO_2), 136.6 (Ph-C), 128.4 (Ph-C), 128.0 (Ph-C), 127.9 (Ph-C), 109.6 (CCl_3), 81.2 (C(OH)), 65.9 (OCH_2), 40.2 (CH_2), 21.5 (CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{13}H_{15}{}^{35}Cl_3N_2NaO_4$ $[M+Na]^+$ 390.9990, found 390.9993; m.p = 147-148 °C; $[\alpha]_D{}^{20}$ -30.0 (*c* 0.03, $CHCl_3$).

Compound 445 or 446



To a solution of benzyl (*R*)-2-(4,4,4-trichloro-3-hydroxy-3-methylbutanoyl)hydrazine-1-carboxylate **444** (0.270 g, 0.738 mmol) in THF (4 mL) was added 2M NaOH (aq.) (1.48 mL, 2.95 mmol) under nitrogen, and the solution was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. This solution was acidified to pH 2, washed three times with pH 2 buffer and the organic fractions were dried over Na_2SO_4. The solvent was removed *in vacuo* to give the product as a colourless oil (0.100 g, 49%). This compound was difficult to purify so it was used directly in the next step as a crude mixture.

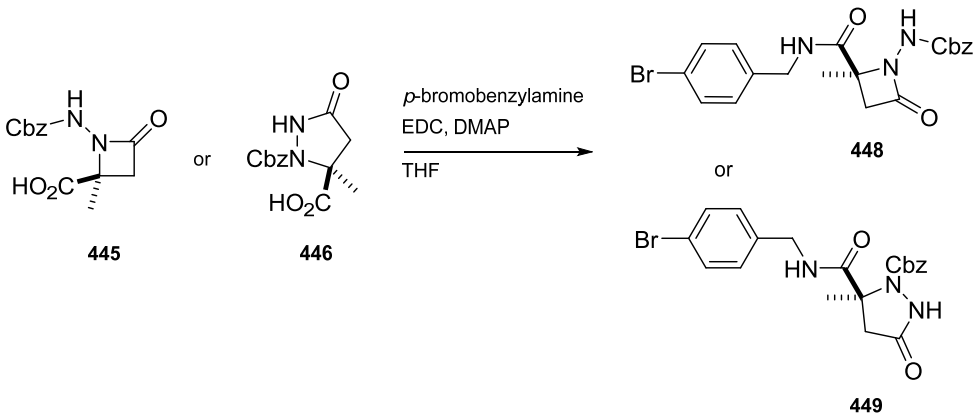
448 or 449 (X = Cl)



To a solution of crude unknown cyclic acid **445** or **446** (0.220 g, 0.791 mmol) from the previous step in dry THF (5 mL) was added EDCI.HCl (0.303 g, 1.58 mmol), DMAP (0.193 g, 1.58 mmol) and *p*-chlorobenzylamine (0.190 mL, 1.58 mmol) and stirred at room temperature under nitrogen overnight. The mixture was then

partitioned between EtOAc and pH 2 buffer and the organic layer was washed with pH 2 buffer three times. The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 to 8:2 to 1:1 petroleum ether/EtOAc) to yield product as a colourless oil (70 mg, 28%). ν (cm^{-1}); 3263 (br, N-H stretch), 1787 (C=O stretch), 1718 (C=O stretch), 1649 (C=O stretch), 1244 and 1041 (C-O stretch), 733 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.04 (1H, s, NHN), 7.81 (1H, s, CH_2NH), 7.43-7.09 (9H, m, Ar-H), 5.15 (1H, d, *J* 12, C*H*HO), 5.05 (1H, d, *J* 11.5, CH*H*O), 4.45-4.31 (2H, m, CH_2NH), 3.00 (1H, d, *J* 15, C*H*HCO), 2.77 (1H, d, *J* 15, CH*H*CO), 1.61 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1 (CONH), 168.3 (CH_2CO), 157.1 (OCONH), 136.6, 134.7, 133.3, 129.3, 129.0, 128.9, 128.8, 128.5 (Ar-C), 68.9 (CH_2O), 65.6 (C(CH_3)), 47.8 (CH_2CO), 42.9 (CH_2NH), 13.7 (C(CH_3)); HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{20}{}^{35}ClN_3NaO_4$ $[M+Na]^+$ 424.1035, found 424.1037; $[\alpha]_D{}^{20}$ -115 (*c* 0.45, $CHCl_3$).

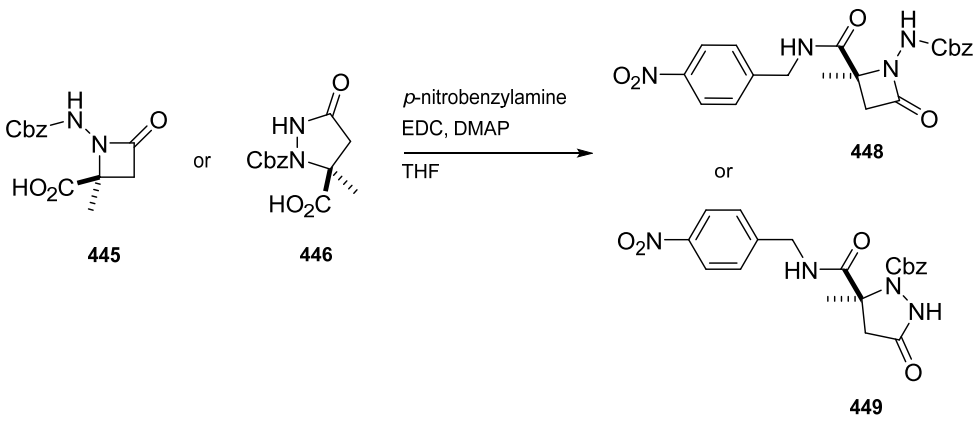
448 or 449 (X = Br)



To a solution of crude unknown cyclic acid **445** or **446** (0.115 g, 0.414 mmol) from the previous step in dry THF (3 mL) was added EDCI.HCl (0.159 g, 0.828 mmol), DMAP (0.101 g, 0.828 mmol) and *p*-bromobenzylamine (0.100 mL, 0.828 mmol) and stirred at room temperature under nitrogen overnight. The mixture was then partitioned between EtOAc and pH 2 buffer and the organic layer was washed with

pH 2 buffer three times. The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (4:6 to 3:7 petroleum ether/EtOAc) to yield the product as a colourless oil (24 mg, 13%). ν (cm^{-1}); 3265 (br, N-H stretch), 1789 (C=O stretch), 1720 (C=O stretch), 1653 (C=O stretch), 1248 and 1043 (C-O stretch), 748 (C-Br stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.00 (1H, s, NHN), 7.47-7.27 (9H, m, Ar-H), 7.15 (1H, d, *J* 7.5, CH_2NH), 5.15 (1H, d, *J* 12, C*H*HO), 5.06 (1H, d, *J* 12, CH*H*O), 4.43-4.31 (2H, m, C*H*$_2$NH), 3.01 (1H, d, *J* 15, C*H*HCO), 2.79 (1H, d, *J* 15, CH*H*CO), 1.62 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9 (CONH), 168.0 (CH_2CO), 156.9 (OCONH), 137.1, 134.5, 131.7, 129.6, 128.9, 128.8, 128.5, 121.3 (Ar-C), 68.9 (CH_2O), 65.5 (*C*(CH_3)), 47.8 (*C*H_2CO), 42.9 (CH_2NH), 18.4 (C(*C*H_3)); HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{20}{}^{79}BrN_3NaO_4$ $[M+Na]^+$ 468.0529, found 468.0525; $[\alpha]_D{}^{20}$ -101 (*c* 0.42, $CHCl_3$).

448 or 449 (X = NO_2)

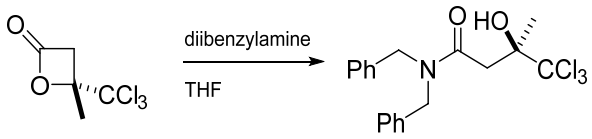


445 446

To a solution of crude unknown cyclic acid **445** or **446** (0.150 g, 0.540 mmol) from the previous step in dry THF (3 mL) was added EDCI.HCl (0.207 g, 1.08 mmol), DMAP (0.132 g, 1.08 mmol), *p*-nitrobenzylamine hydrochloride (0.203 g, 1.08 mmol), trimethylamine (0.300 mL, 2.16 mmol) and stirred at room temperature under nitrogen overnight. The mixture was then partitioned between EtOAc and pH 2 buffer and the organic layer was washed with pH 2 buffer three times. The organic fractions

were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (100% EtOAc) to yield product as a colourless oil (38 mg, 17%). ν (cm^{-1}); 3260 (br, N-H stretch), 1784 (C=O stretch), 1715 (C=O stretch), 1651 (C=O stretch), 1249 and 1040 (C-O stretch), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.20 (1H, s, NHN), 8.21-8.19 (2H, m, Ar-H), 7.46-7.28 (7H, m, Ar-H), 7.07 (1H, s, CH_2NH), 5.19 (1H, d, *J* 12, C*H*HO), 5.13 (1H, d, *J* 12, CH*H*O), 4.59-4.45 (2H, m, CH_2NH), 3.06 (1H, d, *J* 15, C*H*HCO), 2.86 (1H, d, *J* 15, CH*H*CO), 1.66 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1 (CONH), 167.7 (CH_2CO), 157.0 (OCONH), 147.3, 145.5, 134.4, 129.0, 128.8, 128.44, 128.41, 123.9 (Ar-C), 69.1 (CH_2O), 65.4 ($C(CH_3)$), 48.1 (CH_2CO), 42.9 (CH_2NH), 18.4 ($C(CH_3)$); HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{20}N_4NaO_6$ $[M+Na]^+$ 435.1275, found 435.1274; $[\alpha]_D^{20}$ -97.7 (*c* 0.26, $CHCl_3$).

(*R*)-*N*,*N*-Dibenzyl-4,4,4-trichloro-3-hydroxy-3-methylbutanamide 453



171 453

To a solution of (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one **171** (0.243 g, 1.20 mmol) in THF (5 mL) was added dibenzylamine (0.460 mL, 2.40 mmol), and the solution was stirred at 60 °C for 88 hours. The solvent was removed *in vacuo* and the residue was passed through a short plug of silica eluting with 85:15 petroleum ether/EtOAc, to yield product as a white solid (0.337 g, 64%). ν (cm^{-1}); 3272 (br, O-H stretch), 1624 (C=O stretch), 1216 (C-O stretch), 758 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64-7.46 (8H, m, Ph-H), 7.41-7.36 (2H, m, Ph-H), 5.09 (1H, d, *J* 14.5, C*H*HN), 4.79 (1H, d, *J* 17, C*H*HN), 4.70 (1H, d, *J* 14.5, CH*H*N), 4.67 (1H, d, *J* 17, CH*H*N), 3.98 (1H, d, *J* 15.5, C*H*HC(OH)), 3.09 (1H, d, *J* 15.5, CH*H*C(OH)),

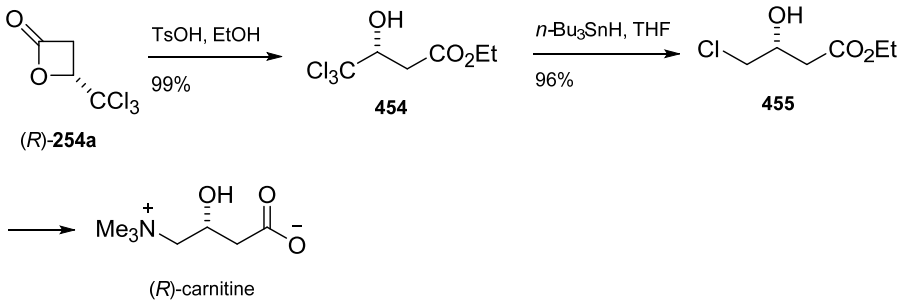
1.86 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9 (CO), 136.4, 135.8, 129.3, 129.0, 128.7, 128.2, 128.0, 126.5 (Ar-C), 107.7 (CCl_3), 82.1 (C(OH)), 50.6, 49.1 (CH_2N), 36.4 (*C*H_2CO), 24.6 (CH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{19}H_{21}{}^{35}Cl_3NO_2$ $[M+H]^+$ 400.0632, found 400.0632; m.p = 113-114 °C; $[\alpha]_D{}^{25}$ -14.7 (*c* 0.38, $CHCl_3$).

Chapter 3

Given our success using (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one (**171**) in the synthesis of both α- and γ-tocopherol, we decided to explore further transformations of this somewhat underused chiral building block. The only other reports in the literature using this lactone in synthesis were discussed previously in section **2.1**.

3.1 (*R*)-4-(Trichloromethyl)-oxetanone 254a

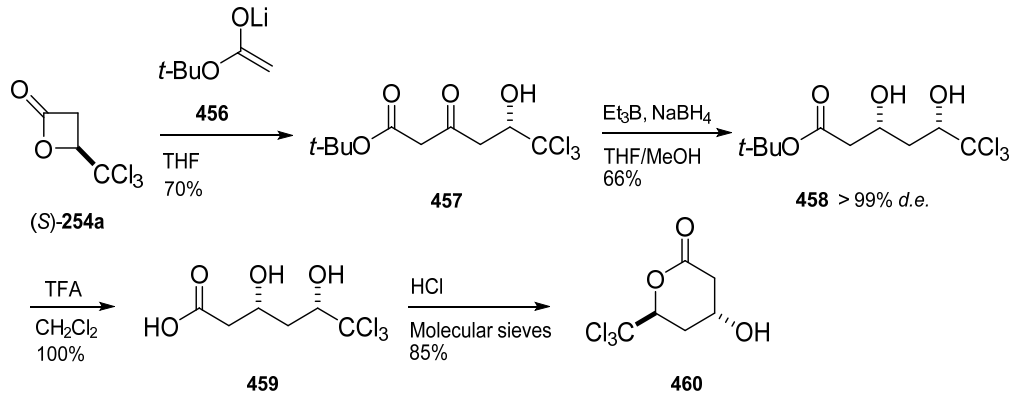
There are more reports in the literature detailing the use of lactone **254a** as an enantiomerically enriched starting material. Song *et al*. used lactone **254a** in the synthesis of ester **455**, a key intermediate in the synthesis of (*R*)-carnitine (Scheme 145).[444]

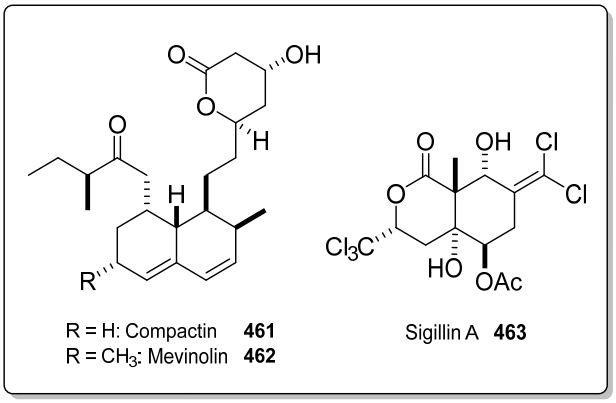


Scheme 145. Reagents and conditions: TsOH (2.0 mol%), EtOH, reflux, 25 h; *n*-Bu_3SnH (2.1 equiv.), THF, reflux, 28 h.

The ethanolysis of **254a** had previously been reported by Wynberg and Staring[445] and no racemisation is observed during the reaction. Selective *bis*-dechlorination was strongly dependent on the temperature – at room temperature the sole product was the singly dechlorinated compound. Conversion of ester **455** into (*R*)-carnitine had been previously reported.[446]

In addition to their work on the Fridel-Crafts ring opening of **254a**, Fujisawa *et al*. also demonstrated that the lactone could be readily opened by ester enolates (Scheme 146).[357]

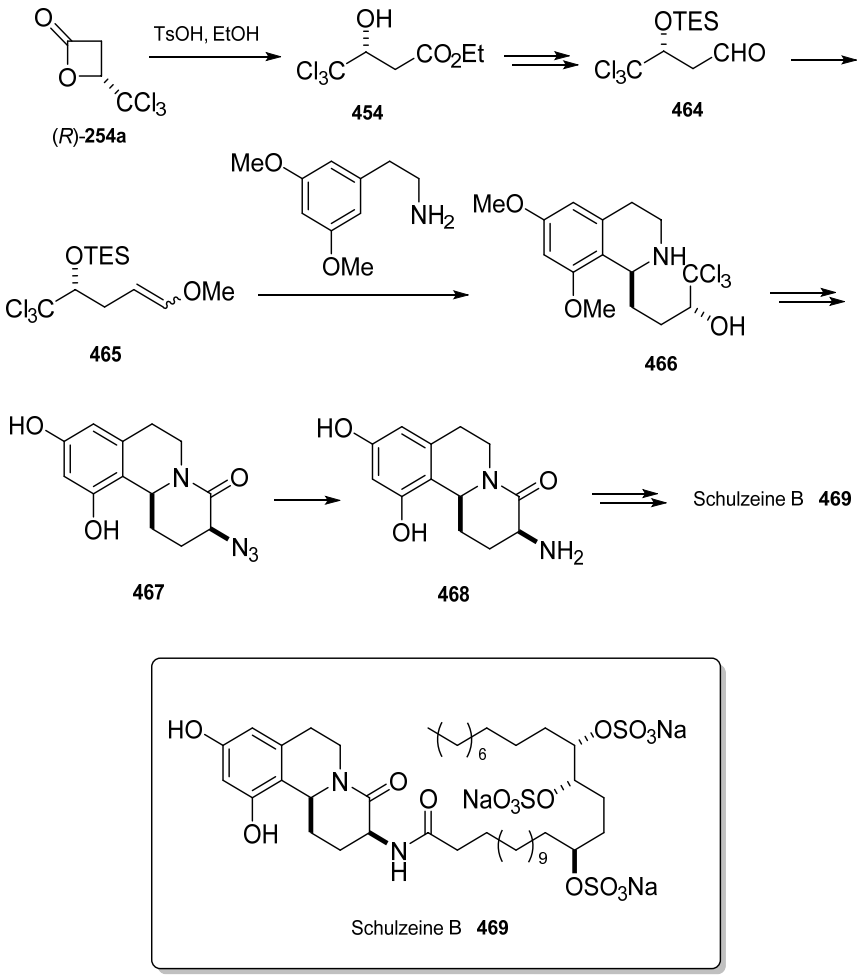




Scheme 146. Reagents and conditions: **456** (5.0 equiv.), THF, -78 °C, 3 h; Et_3B (1.1 equiv.), $NaBH_4$ (1.1 equiv.), -100 °C, 6 h; TFA (100 equiv.), CH_2Cl_2, 0 °C to rt, 12 h; 0.1M HCl (cat.), 4Å molecular sieves, 50 °C, 24 h.

The enolate adduct **457** was elaborated into the β-hydroxy-γ-valerolactone **460**, a useful precursor to Compactin **461** and Mevinolin **462**. Schulz *et al*. used similar methodology in their synthesis of Sigillin A **463**.[447]

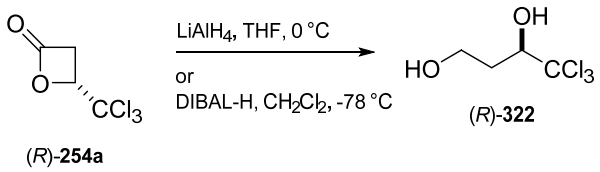
Romo and Liu used (*R*)-lactone **254a** as part of a synthesis of Schulzeine B (Scheme 147). The tetrahydroisoquinoline **466** was obtained as a separable mixture of diastereoisomers from the Pictet-Spengler reaction[448] of **465** and eventually subjected to modified Corey-Link conditions to yield the δ-lactam **467**.



Scheme 147. Synthesis of Schulzeine B.

3.2 The Synthesis of (*R*)-dihydrocitronellol

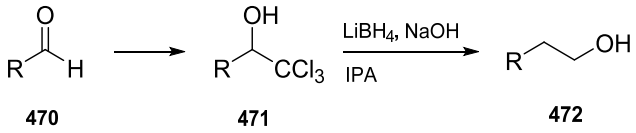
We were most interested in reports that lactone **254a** could be directly reduced using $LiAlH_4$ (Wynberg *et al.*)[445] or using DIBAL-H (Fujisawa *et al.*),[358] to yield the diol **322** (Scheme 148).



Scheme 148. Direct reduction of lactone **254a**.

Both Wynberg and Fujisawa reported that the high enantiomeric excess of **254a** was unchanged by the reduction.

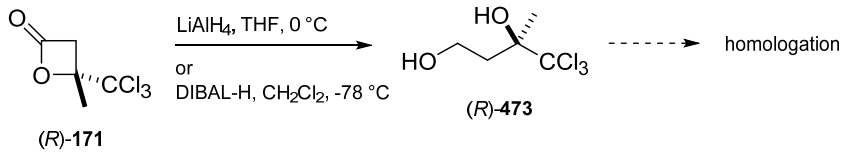
During the course of this research, Snowden *et al*. published the one-carbon homologation of aldehydes **470**, using a Jocic reaction with a hydride nucleophile (Scheme 149).[350]



470 **471** **472**

Scheme 149. One-carbon homologation of trichlorocarbinols. Reagents and conditions: $LiBH_4$ (4.0 equiv.), NaOH (3.0 equiv.), IPA, 40 °C, 16-24 h.

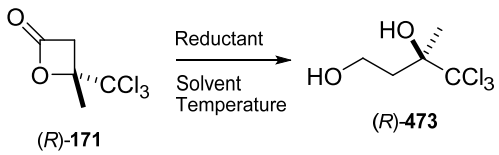
Given that the authors only used secondary trichloroalcohol substrates they could not study the stereochemical outcome of the reaction. We imagined that lactone **171** could be reduced in the same way as lactone **254a**, to yield an enantiomerically enriched, tertiary trichlorocarbinol **473** (Scheme 150).



(*R*)-**171** (*R*)-**473**

Scheme 150. Proposed reduction of lactone **171**.

It was expected that the diol **473** would undergo the same Jocic reaction when subjected to the conditions described by Snowden *et al*. to yield an isoprenoid compound, potentially in high enantiomeric excess. Table 32 shows a brief optimisation study for the direct reduction of lactone **171**.



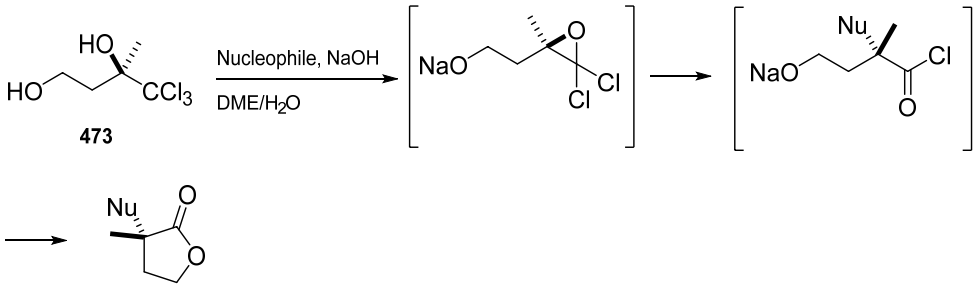
(*R*)-**171** (*R*)-**473**

entry	reductant	solvent	temperature (°C)	time (h)	yield (%)
1	$LiAlH_4$	THF	0	1	85
2	DIBAL-H	CH_2Cl_2	23	16	55
3	$NaBH_4$	MeOH	23	16	0
4	$LiBH_4$	THF	0	1	67
5	$LiBH_4$	THF	0	0.5	99

Table 32. Optimisation of conditions for the reduction of lactone **171**. 3.0 Equivalents of the reductant were used in each entry.

Using $LiAlH_4$ as described by Wynberg (entry **1**) gave the diol **473** in good yield. However, unidentified side products were present in the crude mixture so the compound required purification by column chromatography. We imagined that there should be conditions that would yield diol **473** without the need for extra purification, so alternative reductants were screened. The use of DIBAL-H (entry **2**) gave a less satisfactory yield of the diol. The reaction with $NaBH_4$ yielded unreacted starting materials only. $LiBH_4$ yielded diol **473** after 30 minutes at 0 °C, in essentially quantitative yield without the need for further purification (entry **5**). Gram-quantities of the diol were accessible using this procedure.

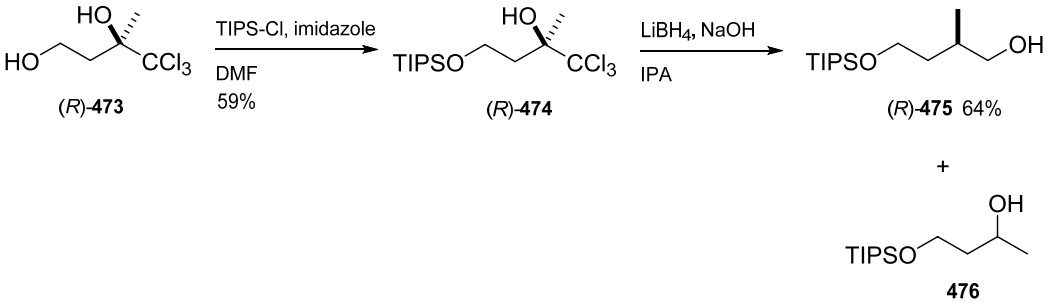
With the diol **473** in hand, we first wondered if it would undergo a Jocic reaction/lactonisation like that reported by Romo *et al*. (Scheme 151).[354]



Scheme 151. Attempted synthesis of α-disubstituted γ-lactones.

p-Methoxyphenol was chosen as the nucleophile, since it had been previously reported by Corey to take part in Jocic reactions of the type in scheme 151.[435] Unfortunately, under the conditions described by Romo *et al*. an unidentifiable mixture was obtained.

In order to prevent side reactions in the homologation reaction of **473**, the primary alcohol was selectively protected with triisopropylsilyl chloride. This group is known to be stable to alkaline conditions.[449] The monoprotected diol **474** was then subjected to the conditions developed by Snowden *et al*. (Scheme 152).



Scheme 152. One-carbon homologation of a tertiary trichlorocarbinol.

The desired alcohol (*R*)-**475** was isolated in 64% yield under the conditions described by Snowden. However, also present in the crude reaction mixture was the secondary alcohol **476**. It was not possible to establish the ratio of **475**:**476** from the crude ^{1}H NMR spectrum since the peaks were overlapping (Figure 19). The formation of **476** can be rationalised using the following mechanistic pathway (Scheme 153).

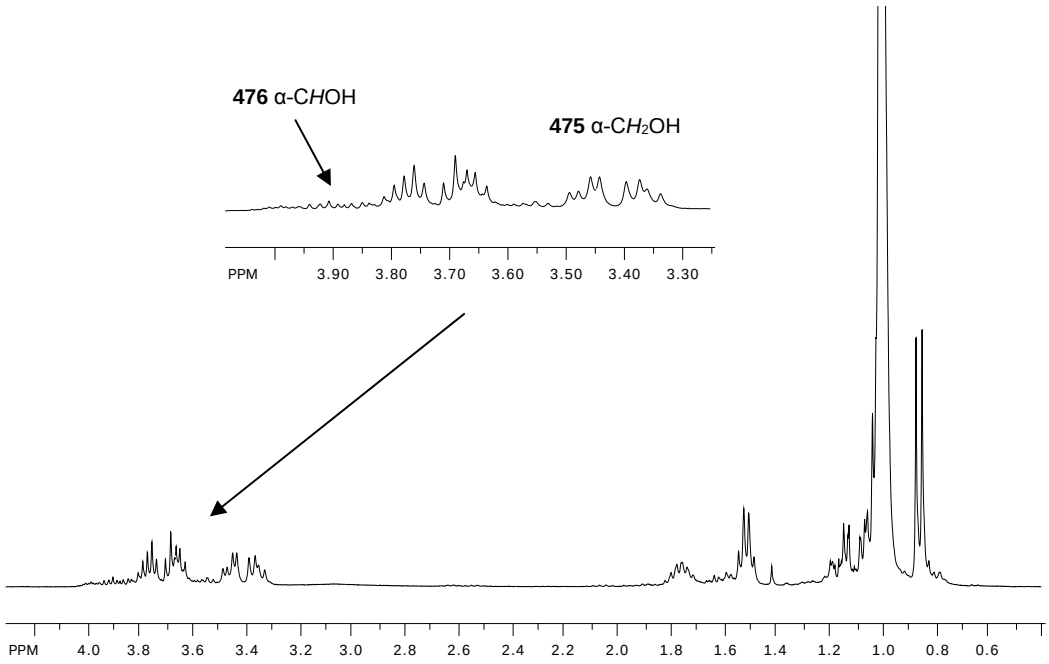
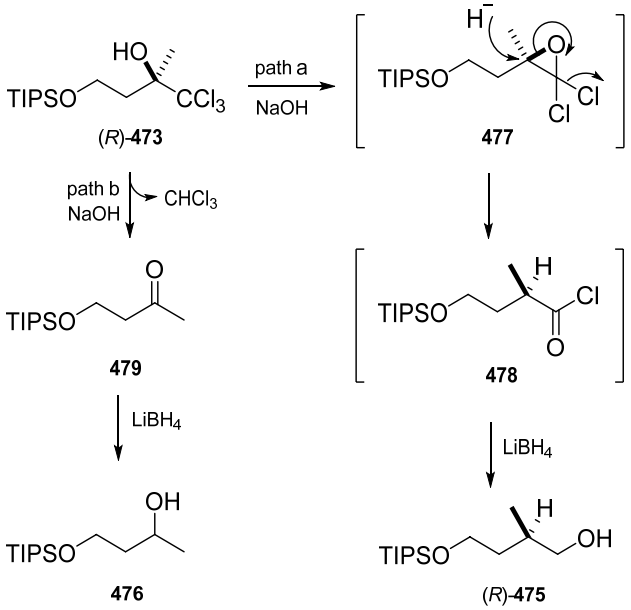


Figure 19. ^{1}H NMR of crude reaction mixture. Inset: magnified region showing α-CH protons.

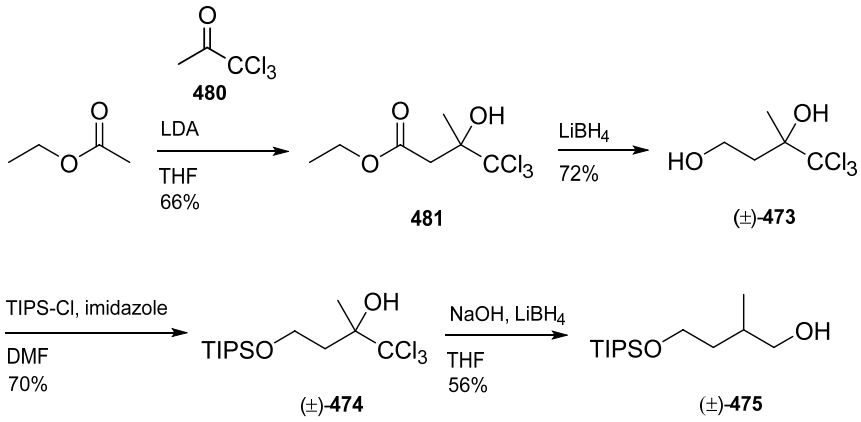


Scheme 153. Reaction pathways leading to the formation of alcohols (*R*)-**475** and **476**.

The predominant pathway must be path a, following the accepted Jocic reaction mechanism to yield the primary alcohol **475.** The formation of secondary alcohol **476** is presumably due to initial elimination of $CHCl_3$ from the trichlorocarbinol (*R*)-**473** to give ketone **479**, which is reduced by $LiBH_4$. Snowden *et al*. reported no such side

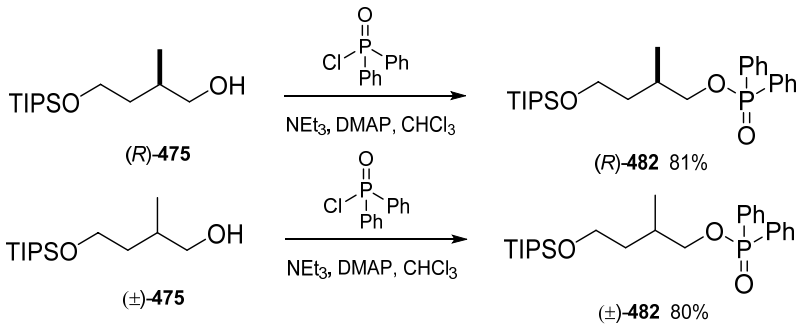
products, since there will not be as great a driving force for elimination of $CHCl_3$ in the corresponding secondary trichlorocarbinols.

Luckily, the primary alcohol (*R*)-**475** was separable from the side product alcohol **476** by column chromatography. In order to measure the *e.e.* of the primary alcohol we first attempted to use the (*R*)- and (*S*)-Mosher's ester derivatives. Unfortunately, the diastereomeric esters showed no difference by ^1H NMR spectroscopy. We therefore turned to HPLC analysis. Scheme 154 describes the racemic synthesis of (±)-**475**. An aldol condensation between ethyl acetate enolate and 1,1,1-trichloroacetone **480** yielded the adduct **481** in moderate yield. The use of $LiAlH_4$ in place of $LiBH_4$ in the following reduction gave a poor yield (34%) of the diol (±)-**473**. Monoprotection of the diol with triisopropylsilyl chloride was carried out in the same manner as for the enantiomerically enriched compound.



Scheme 154. Synthesis of racemic monoprotected diol (±)-**475**.

The reaction of trichlorocarbinol (±)-**474** with $NaOH/LiBH_4$ yielded the alcohol (±)-**475** in comparable yield, along with **476** which was separated by column chromatography. Both the racemate and the enantiomerically enriched alcohols **475** were then converted into the diphenylphosphinate esters (*R*)-**482** and (±)-**482** (Scheme 155).



Scheme 155. Synthesis of phosphonate esters.

Benzoate esters are commonly used for the HPLC analysis of compounds with no chromophore, however other members of the group have had success in separating enantiomers using the phosphonate ester group.

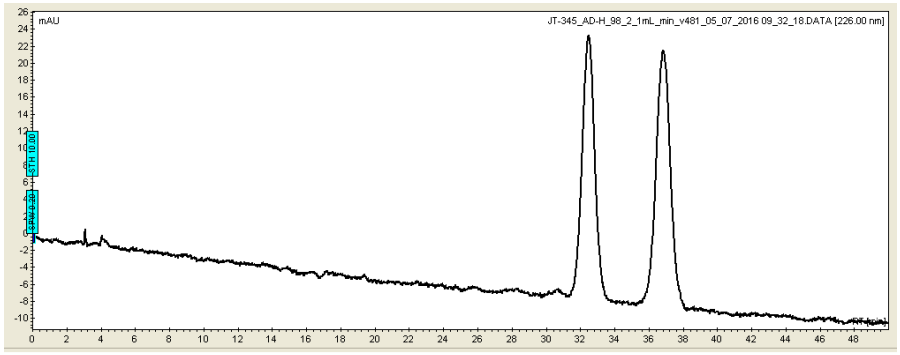


Figure 20. HPLC trace of (±)-**482**.

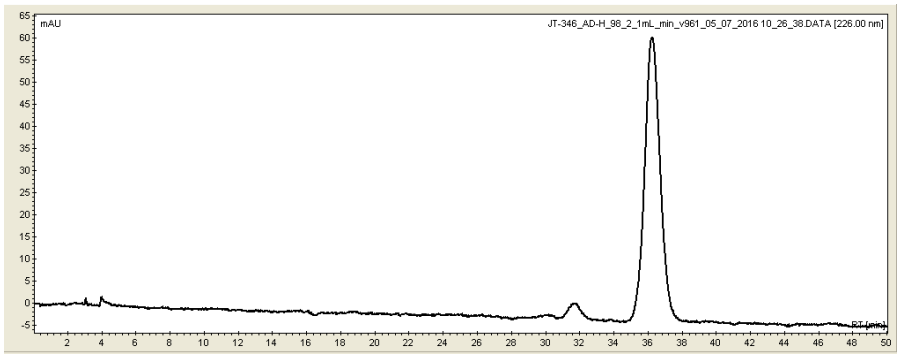
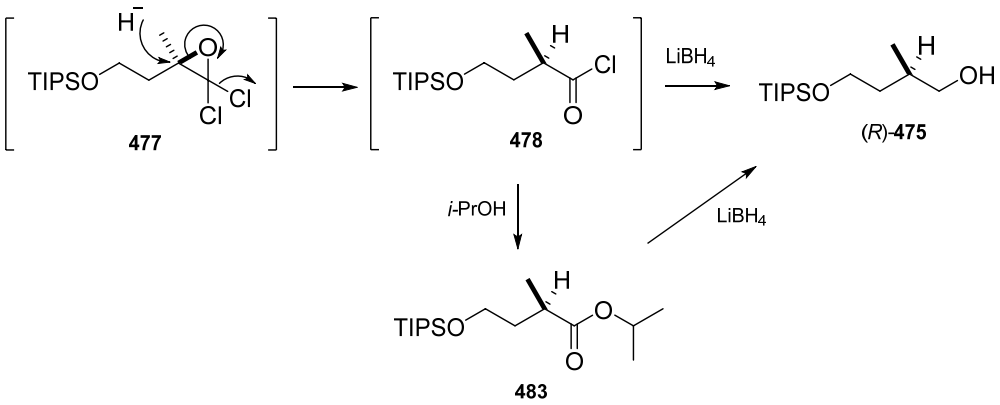


Figure 21. HPLC trace of (*R*)-**482**. Conditions: Daicel Chiralcel AD-H column, 2-propanol : hexane = 98 : 2, 1 mL/min, 225 nm, (*S*) isomer 32.49 min, (*R*)-isomer 36.84 min.

The *e.e.* of phosphonate ester (*R*)-**482** was measured to be 92% (Figures 20 and 21), and the absolute configuration of the alcohol **475** was established as (*R*) by comparison of the measured optical rotation to the literature value. This corresponds to an expected

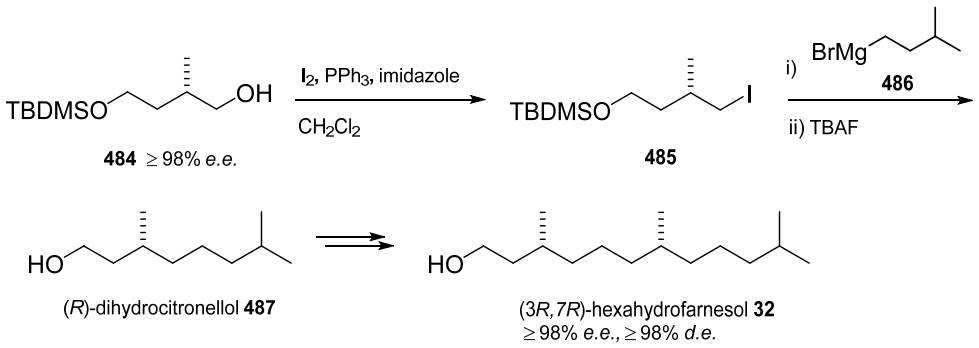
inversion of configuration during the Jocic reaction. Given that the ring-opening of the *gem*-dichloroepoxide **477** is known to be highly stereospecific, the racemisation must be taking elsewhere in the reaction mechanism. Snowden *et al*. reported that isopropyl esters such as **483** were intermediates in the reaction pathway (Scheme 156).



Scheme 156. Formation of an isopropyl ester intermediate **483**.

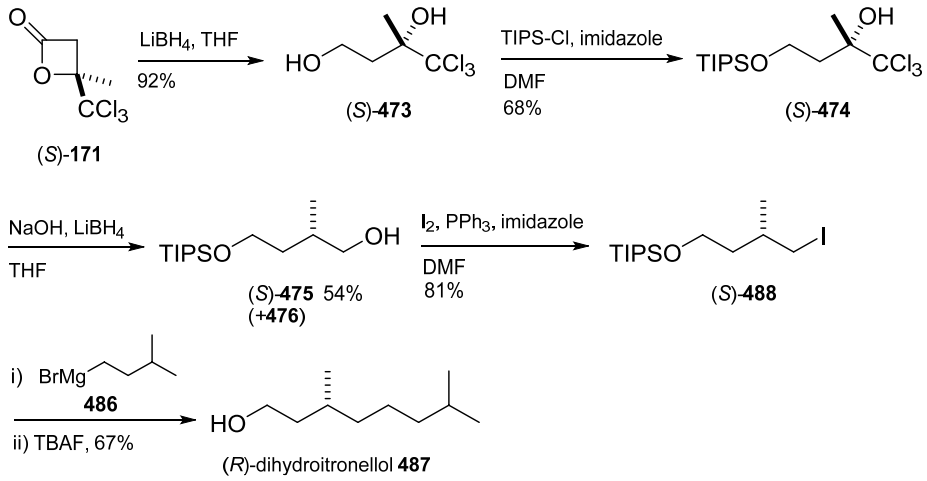
This intermediate was also identified during our work. Both the acid chloride **478** and the ester **483** will be prone to enolisation under the alkaline conditions due to the α-protons in each compound, so it seems likely that this is the source of the racemisation taking place in the reaction.

A search in the literature revealed alcohol (*S*)-**484** to be a key intermediate in a stereoselective synthesis of (3*R*,7*R*)-hexahydrofarnesol **32** by Matsueda *et al*. (Scheme 157).[450] We envisaged that the same sequence of reactions using (*S*)- rather than (*R*)-**475** should yield (*R*)-dihydrocitronellol **487**, and eventually (3*R*,7*R*)-hexahydrofarnesol **32**. We decided to keep triisopropylsilane as the protecting group since we imagined that it should not behave differently to *tert*-butyldimethylsilane (TBDMS) under the reaction conditions shown in scheme 157.



Scheme 157. Synthesis of (3*R*,7*R*)-hexahydrofarnesol **32** by Matsueda *et al.* Reagents and conditions: I_2 (1.3 equiv.), PPh_3 (1.2 equiv.), imidazole (1.3 equiv.), CH_2Cl_2, rt, 16 h; **486** (2.0 equiv.), $CuCl_2$ (3.0 mol%), 1-phenyl-1-propyne (0.15 equiv.), THF, rt, 2 h; TBAF (2.0 equiv.), THF, rt, 3 h.

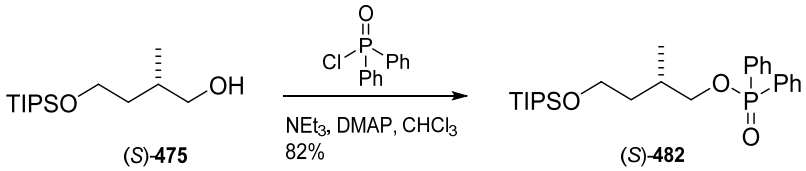
Scheme 158 shows the synthesis of (*R*)-dihydrocitronellol **487**. The same sequence of reactions previously developed were used to synthesise (*S*)-alcohol **475**, starting from the (*S*)-enantiomer of lactone **171**. The conversion of (*S*)-**475** into (*R*)-dihydrocitronellol **487** was then carried out according to Matsueda *et al*.



Scheme 158. Synthesis of (*R*)-dihydrocitronellol **487**.

It was imagined that the racemisation observed during the Jocic reaction to form alcohol (*S*)-**475** might be suppressed by lowering the reaction temperature. Accordingly, when the reaction was carried out at 0 – 2 °C no racemisation was observed by chiral HPLC (Figure 23). However, the reaction was extremely sluggish and only went to 25% conversion after four days. The reaction was similarly slow at

10 °C. When the reaction was carried out at room temperature the *e.e.* appears to increase and none of the (*R*)-enantiomer could be observed (Figure 24). An increased reaction time (24 hours) was required to ensure full conversion. An attempt was made to convert (±)-dihydrocitronellol **487** into its phosphonate ester for a direct measurement of the stereochemical purity of the (*R*)-dihydrocitronellol **487** product, but the enantiomers were inseparable by chiral HPLC.



Scheme 159. Synthesis of phosphonate ester (*S*)-**482**.

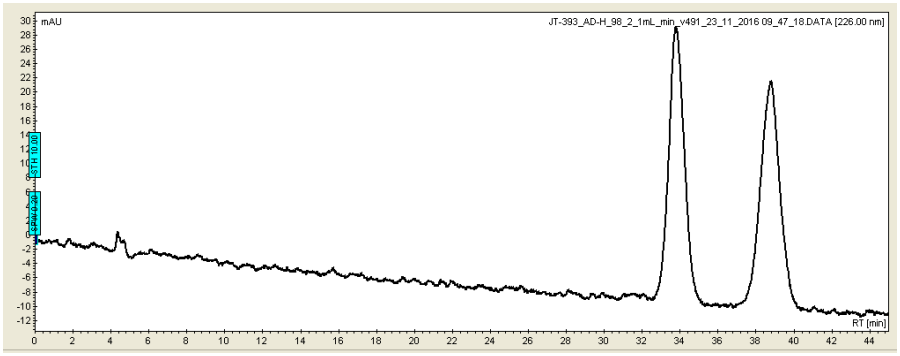


Figure 22. HPLC trace of the phosphonate ester (±)-**482**.

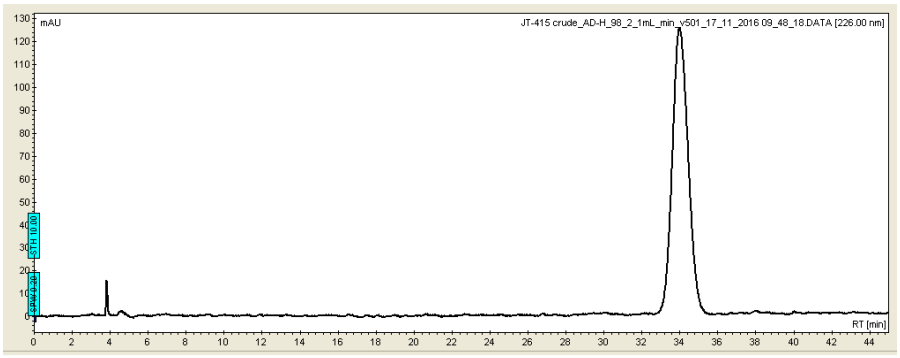


Figure 23. HPLC trace of the phosphonate ester (*S*)-**482** (0 °C reaction temperature).

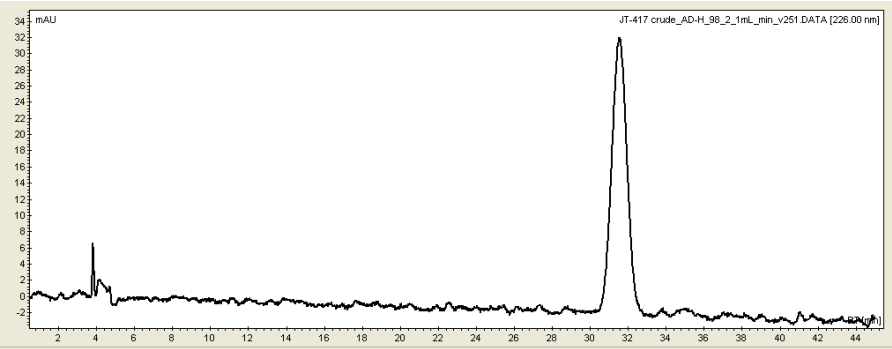
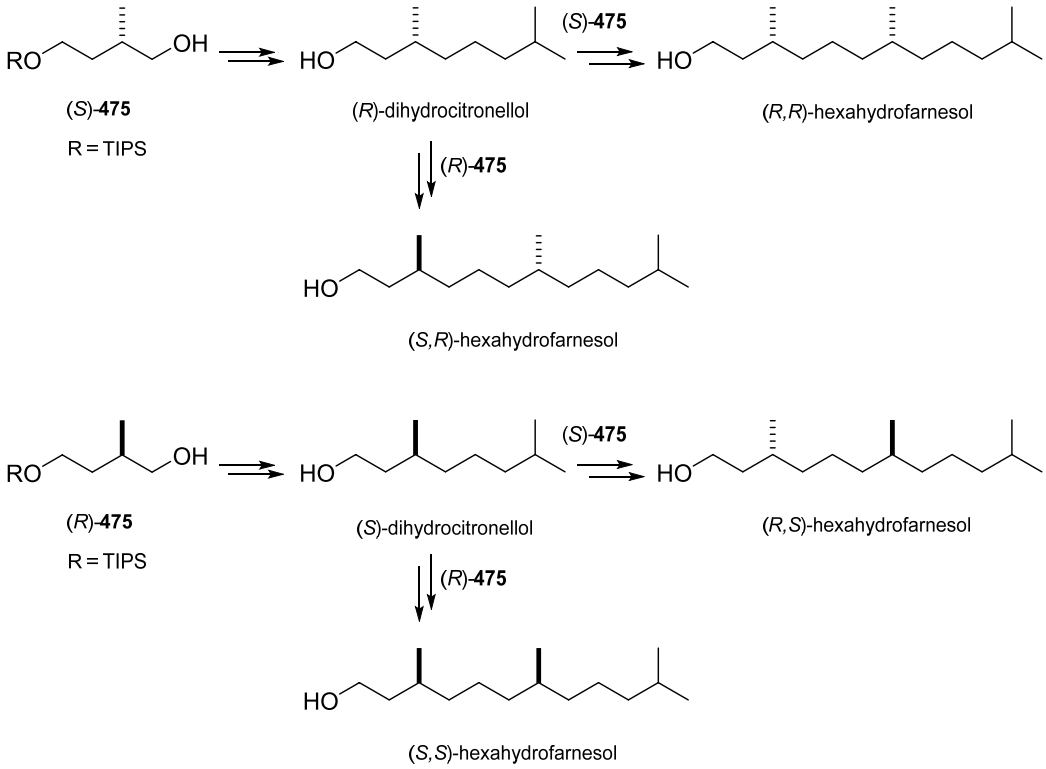


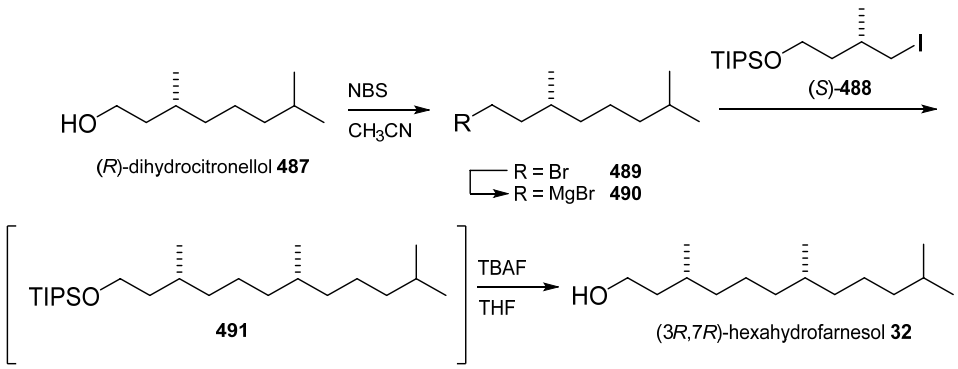
Figure 24. HPLC trace of the phosphonate ester (*S*)-**482** (room temperature reaction). Conditions: Daicel Chiracel AD-H column, 2-propanol : hexane 98 : 2, 1 mL/min, 225 nm, (*S*) isomer 33.78 min, (*R*) isomer 38.80 min.

Using this successive Grignard coupling strategy, all four stereoisomers of hexahydrofarnesol ought to be accessible in high *e.e.* and *d.e.* (Scheme 160). This strategy was previously used by Barner *et al.* where the source of chirality was a natural γ-lactone.[168, 170]



Scheme 160. Potential stereoselective synthesis of all four stereoisomers of hexahydrofarnesol.

In this way, (*R*)-dihydrocitronellol **487** was converted into (3*R*,7*R*)-hexahydrofarnesol **32** (Scheme 161). Unfortunately, the second Grignard coupling step was low yielding and the desired hexahydrofarnesol **32** was contaminated with inseparable side products. Further attempts, preferably on a larger scale, would be required to optimise this step. Nevertheless, this work further demonstrates the usefulness of trichlorolactones such as **171** as chiral building blocks.



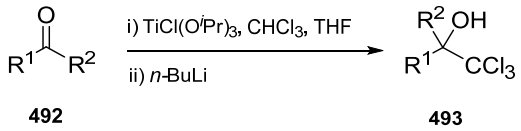
Scheme 161. Completion of the hexahydrofarnesol synthesis.

3.3 Scope of the Reductive Jocic Reaction

We established that the Jocic reaction with a hydride nucleophile developed by Snowden *et al*. produced alcohols in high *e.e*. when enantiomerically pure, tertiary trichlorocarbinols were used as substrates. We were therefore interested to explore the potential generality of the homologation reaction.

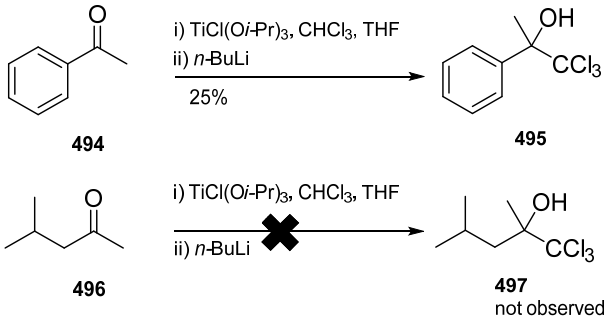
3.3.1 The Synthesis of Tertiary Trichlorocarbinols

Whilst the synthesis of secondary trichlorocarbinols from aldehydes is well established,[235-237, 261] the synthesis of tertiary trichlorocarbinols from ketones is more difficult. This is primarily due to competing enolisation when strong bases are used. Li *et al*. reported the use of organotitanium reagents to prepare tertiary trichlorocarbinols, and high yields were obtained from readily enolisable ketones (Scheme 162). [238]



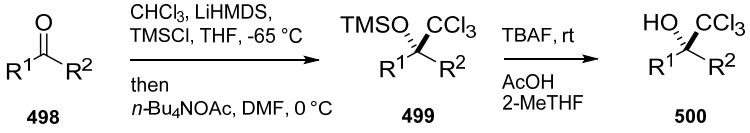
Scheme 162. Reagents and conditions: $CHCl_3$ (5.0 equiv.), *n*-BuLi (5.0 equiv.), $TiCl(O^iPr)_3$ (2.0 equiv.), THF, -60 °C, 4 h. R^1 = aryl, vinyl; R^2 = alkyl.

This seemed to be a potential general procedure. Unfortunately, in this project when the simple ketones **494** and **496** were subjected to the reported conditions the reaction either failed or was low yielding (Scheme 163). Alternative procedures were therefore sought.



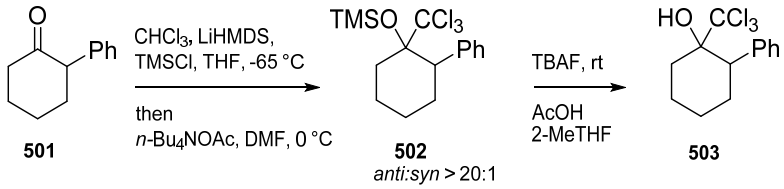
Scheme 163. Attempted synthesis of tertiary trichlorocarbinols.

Henegar and Lira developed a protocol for *in situ* generation of TMS-CCl_3 and addition to carbonyl compounds (Scheme 164).[256, 379]



Scheme 164. Synthesis of trichlorocarbinols using *in situ* generated TMS-CCl_3. R^1 = aryl, alkyl; R^2 = H, alkyl.

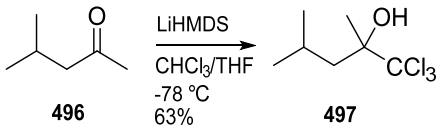
In addition, they showed that using the bulky TMS-CCl_3 nucleophile gave good diastereoselectivity for substituted cyclohexanone substrates (Scheme 165).



Scheme 165. Diastereoselective synthesis of trichlorocarbinol **503**.

As expected, the CCl_3 group preferentially added *anti* to the 2-phenyl substituent. Because a variety of substituted cyclohexanone compounds are commercially available, we imagined this method might provide a route to diastereomerically enriched trichlorocarbinols such as **503**, as well as general racemic compounds, in order to establish the scope of the Jocic reaction.

The use of identical conditions to those shown in schemes 164 and 165 failed to give any trace of product when **496** was used as the ketone; however, addition of LiHMDS to a solution of ketone **496** and $CHCl_3$ in THF yielded the desired trichlorocarbinol **497** in an acceptable yield of 63% (Scheme 166).



Scheme 166. Synthesis of tertiary trichlorocarbinol **497**.

In this way a variety of alkyl trichlorocarbinols were synthesised (Figure 25). Aryl ketones were not considered suitable substrates at this point due to their low yielding conversion into trichlorocarbinols by this method. The yields for compounds **505a-i** ranged from moderate to good. The method of Aggarwal[236] used for compound **505f** failed when applied to any other substrate.

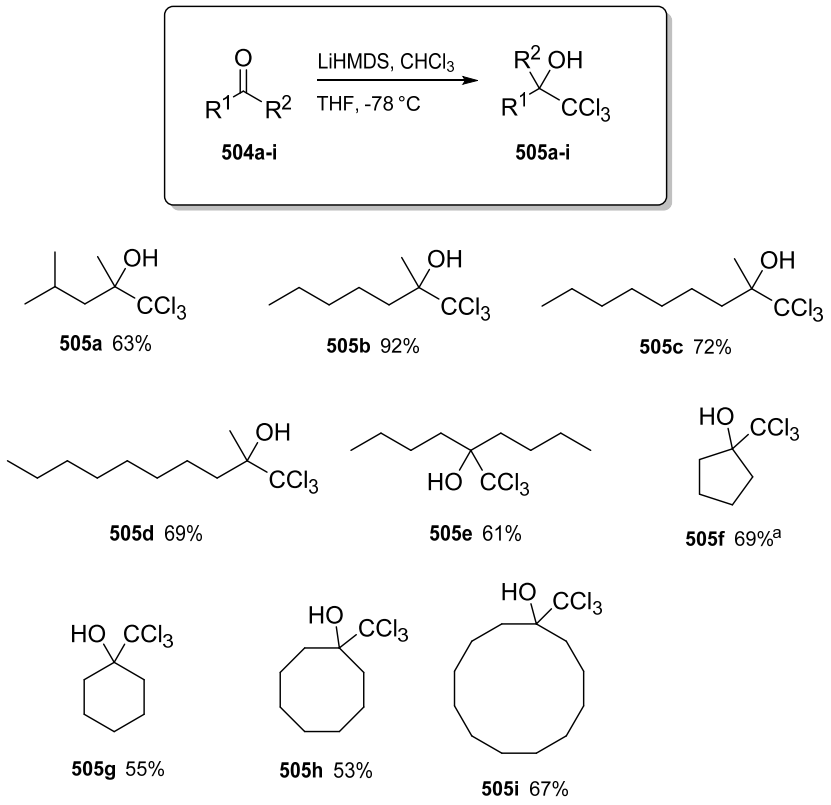
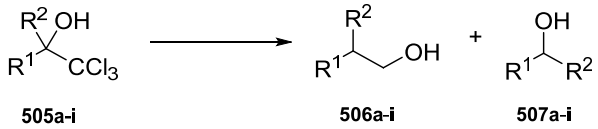


Figure 25. Synthesis of tertiary trichlorocarbinols. [a] This compound was synthesised using the method of Aggarwal *et al*.: $CHCl_3$ (2.0 equiv.), DBU (1.0 equiv.), rt, 16 h.

3.3.2 Jocic Reation using Hydride Nucleophile

With the trichlorocarbinols **505a-i** in hand, we subjected them to the reductive Jocic reaction conditions we had previously developed. The results are shown in Table 33. Unfortunately, most of the substrates were inseparable from the secondary alcohol **507** side product. The low crude yield of **506a** is likely due to the volatility of the low molecular weight alcohol. None of the linear alkyl substrates (**a**-**e**) tested could be separated from the secondary alcohol side product. The increased steric hindrance of **505e** is presumably responsible for the higher proportion of side product, due to a greater driving force for elimination of $CHCl_3$. Smaller rings (cyclopentyl, **505f** and cyclohexyl, **505g**) gave more favourable ratios than the larger rings (cyclooctanyl, **505h** and cyclododecanyl, **505i**). However, it was possible to isolate the primary alcohol **506i** cleanly in 49% yield.



entry	ratio 506:507[a]	506 yield (%)	entry	ratio 506:507[a]	506 yield (%)
a	70:30	14[b]	**f**	95:5	70[c]
b	82:18	69[b]	**g**	73:17	76[b]
c	77:23	65[b]	**h**	21:79	82[b]
d	82:18	90[b]	**i**	66:34	49
e	45:55	90[b]			

Table 33. Reagents and conditions: $LiBH_4$ (4.0 equiv.), NaOH (3.0 equiv.), IPA, rt, 24 h. [a] Determined by analysis of the ^1H NMR spectrum of the crude material. [b] Crude yield: compound **506** was inseparable from compound **507**. [c] Crude yield: compound was difficult to isolate due to its volatility.

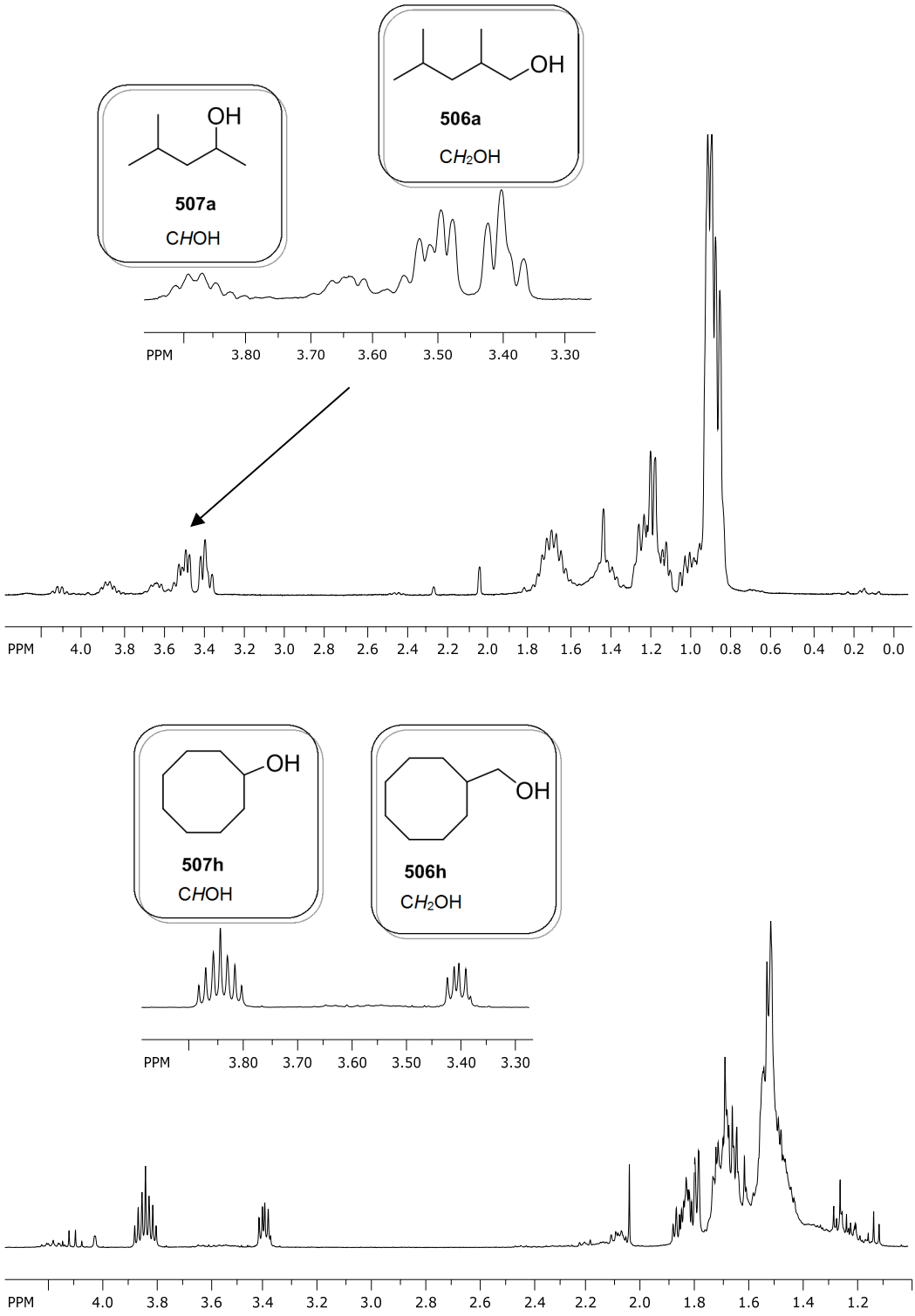


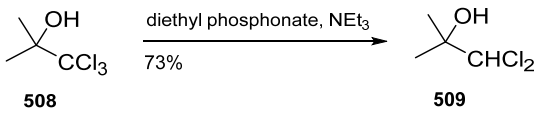
Figure 26. Top: ^{1}H NMR spectrum of entry **a** crude mixture. Bottom: ^{1}H NMR spectrum of entry **h** crude mixture.

3.4 Dichlorocarbinols as Alternative Substrates

We established that hydride could take part in a Jocic reaction with tertiary trichlorocarbinols to yield various branched alcohols, in an overall one-carbon homologation from the starting material ketone. However, the main drawback appeared to be the formation of a secondary alcohol which was often inseparable from the desired primary alcohol. The ratio of the two products was also found to be in favour of the secondary alcohol for the more hindered substrates. We imagined that using the corresponding dichlorocarbinols might provide a solution to this issue, since the elimination of dichloromethane from the compound will be much less favourable and therefore slower than the elimination of chloroform.

3.4.1 Literature Syntheses and Reactions of Dichlorocarbinols

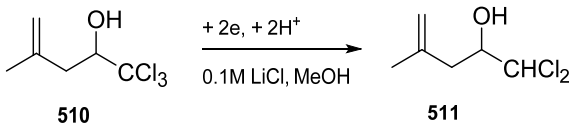
Methods for the synthesis of tertiary dichlorocarbinols in the literature are scarce. Ohshiro *et al*. used diethyl phosphonate-triethylamine to reduce trichlorocarbinol **508** to the corresponding dichlorocarbinol **509** (Scheme 167).[451]



508 **509**

Scheme 167. Reagents and conditions: diethyl phosphonate (4.0 equiv.), NEt_3 (3.0 equiv.), 80 °C, 12 h.

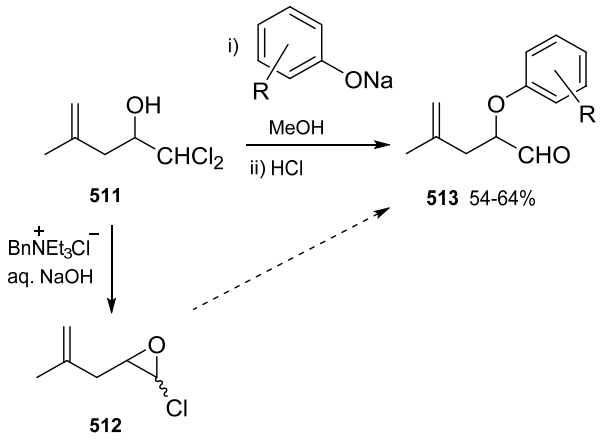
The trichloromethyl group can also be electrochemically reduced selectively to the dichloromethyl group (Scheme 168).[452]



510 **511**
yield not given

Scheme 168. Electrochemical reduction of trichloromethyl group. Mercury cathode, -1.6V working potential versus saturated calomel electrode.

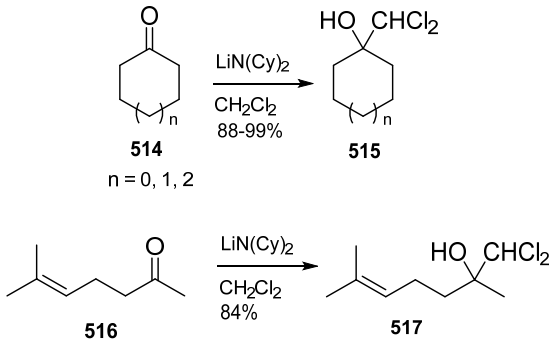
Fechtel *et al*. synthesised **511** in this way and used it in a Jocic-type reaction, with a phenoxide nucleophile (Scheme 169).[336]



Scheme 169. Synthesis of α-aryloxy-aldehydes.

Although this reaction was carried out on a secondary substrate, and we were interested in tertiary substrates, we still felt it was promising for our proposal. Additionally, the authors managed to isolate the chloroepoxide **512**, which provides further evidence for these epoxides as intermediates in the general Jocic reaction mechanism.

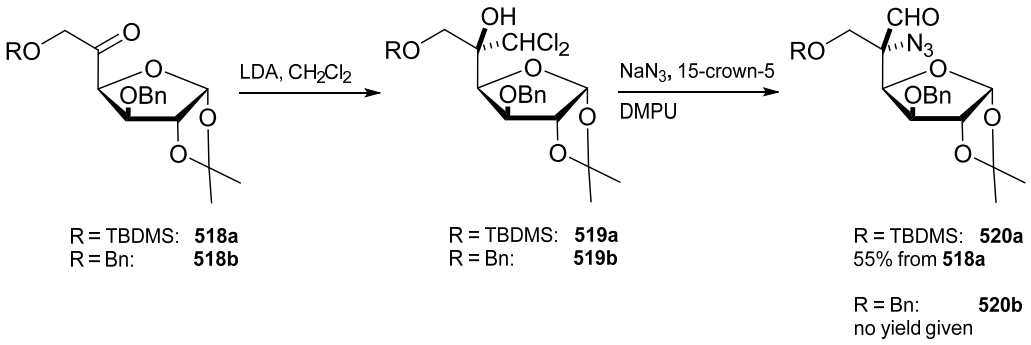
Probably the most straightforward method for the synthesis of dichlorocarbinols is the addition of dichloromethyl anion, much like the procedures discussed in Chapter 1 for the synthesis of trichlorocarbinols. Taguchi *et al*. described a practical synthesis of polyhalomethyl-lithium adducts (Scheme 170).[453, 454]



Scheme 170. Reagents and conditions: Lithium dicyclohexylamide (2.0 equiv.), CH_2Cl_2, -78 °C, 1 h.

The lesser acidity of dichloromethane compared to chloroform requires that a stronger base than LiHMDS be used. Lithium dicyclohexylamide, lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidine all gave similar results. The steric bulk of these bases and the low temperature used helps to minimise enolisation side reactions. In addition to dichloromethane, the authors found that dibromomethane, diiodomethane and bromoform all gave the adducts in useful yields.

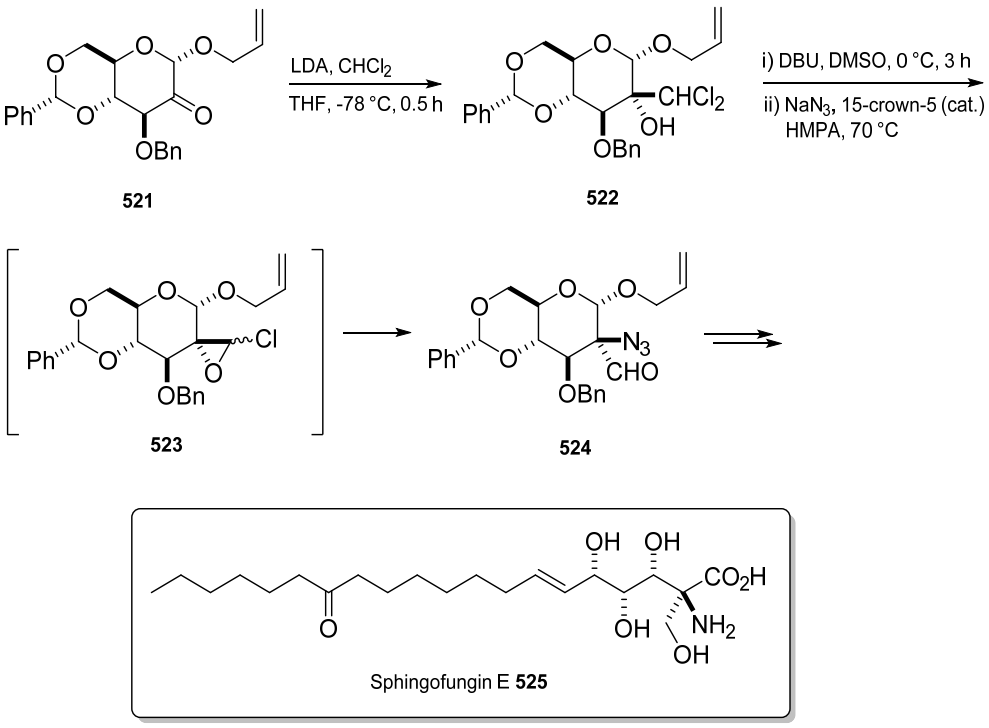
Deloisy *et al*. used this procedure to synthesise a sugar-derived dichlorocarbinol in stereoselective fashion, which then underwent a Jocic reaction with sodium azide (Scheme 171).[455]



Scheme 171. Stereoselective synthesis of α-azido aldehyde **520a** and **520b**. Reagents and conditions: LDA (4.0 equiv.), CH_2Cl_2 (4.0 equiv.), THF, -78 °C to rt; NaN_3 (10 equiv.), DMPU (5.0 equiv.), 15-crown-5 (0.1 equiv.), 70 °C. DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

The addition of dichloromethyllithium to the ketone **518a** took place selectively to yield dichlorocarbinol **519a**, which in turn was converted into the α-azido aldehyde **520a** by treatment with sodium azide. The same reaction sequence with R = Bn yielded **520b** as a 2:1 mixture of diastereoisomers isomeric at C-5.

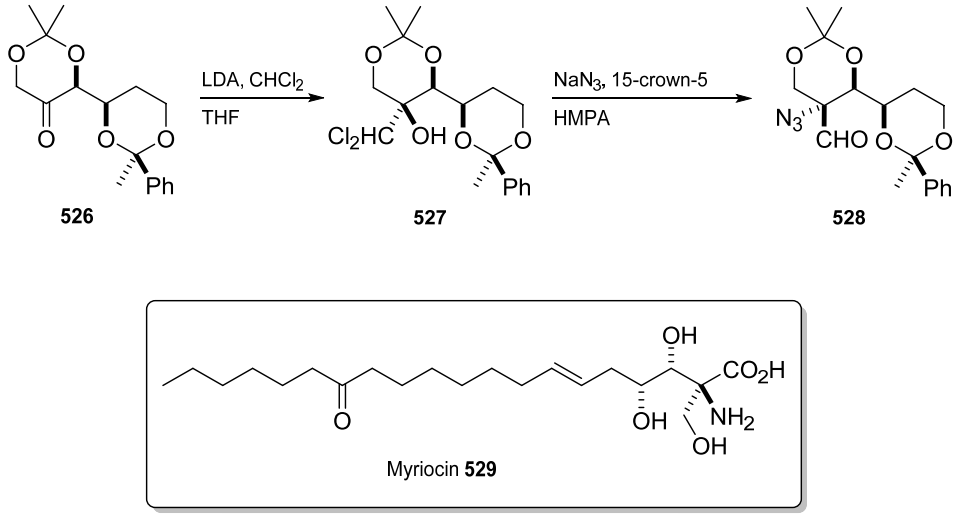
Shiozaki and Nakamura used similar chemistry as part of a synthesis of Sphingofungin E (**525**, Scheme 172).[456]



Scheme 172. Synthesis of Sphingofungin E.

Addition of dichloromethyllithium to the pyranose **521** took place diastereoselectively, due to steric hindrance from the anomeric axial allyl group. None of the C-2 epimer was observed.

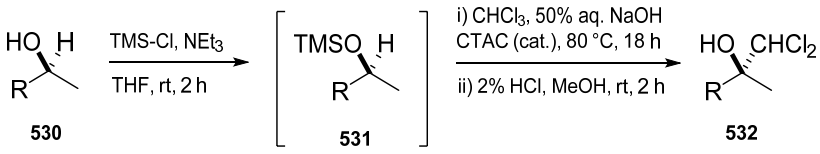
Yoshikawa *et al*. described a similar strategy during the synthesis of the structurally similar antifungal compound Myriocin (**529**, Scheme 173).[457]



Scheme 173. Reagents and conditions: LDA (2.0 equiv.), CH_2Cl_2 (10 equiv.), -78 °C, 15 min; NaN_3 (5.0 equiv.), 15-crown-5 (0.5 equiv.), HMPA, 100 °C, 2 h.

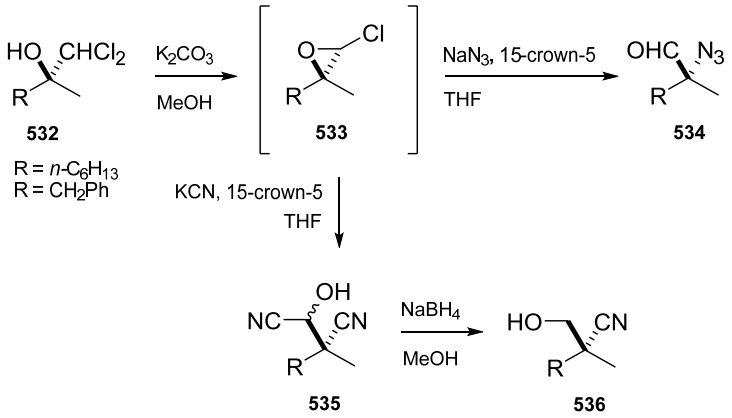
The observed diastereoselectivity of dichloromethyllithium addition in this example arises due to steric hindrance from the bulky 1,3-benzylidene group at the C-4 position.

Masaki *et al*. reported that dichlorocarbene, generated from a $CHCl_3$/ aq. NaOH/ phase transfer catalyst system, took part in a C-H insertion reaction with chiral secondary alcohols (Scheme 174).[458, 459]



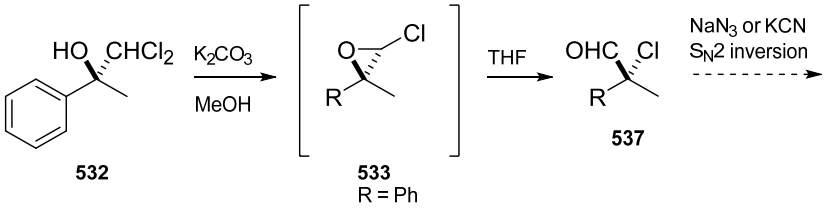
Scheme 174. Insertion of dichlorocarbene. CTAC = cetyltrimethylammonium chloride. R = *n*-C_6H_{13}, CH_2Ph, Ph

This report particularly interested us since the authors claimed that the insertion was completely stereospecific, allowing the synthesis of enantiomerically pure dichlorocarbinol compounds **532** which were previously inaccessible. The authors then demonstrated that these compounds would undergo a Jocic reaction with either sodium azide or sodium cyanide, in stereospecific fashion (Scheme 175).



Scheme 175. Reagents and conditions: K_2CO_3 (5.0 equiv.), MeOH, rt, 10 min; NaN_3 (3.0 equiv.), 15-crown-5 (1.0 equiv.), THF, rt, 12 h; KCN (3.0 equiv.), 18-crown-6, THF, rt, 12 h; $NaBH_4$ (5.0 equiv.), MeOH, rt, 10 min.

In this way compounds **534** and **536** were obtained in > 98% *e.e*. The reaction of chloroepoxide **533** with cyanide first yielded the cyanohydrin **535** as a mixture of diastereoisomers, which was reduced to the primary alcohol **536**. Interestingly, when phenyl dichlorocarbinol (R = Ph) was used as the substrate the opposite enantiomer of compounds **534** and **536** was observed. An intramolecular chloride 1,2-shift is one explanation for this double inversion, and the α-chloro-aldehyde **537** was indeed isolated (Scheme 176). An alternative mechanism where the chloroepoxide **533** is opened by chloride nucleophile, then substituted by azide in S_N2 fashion, would also explain this double inversion.

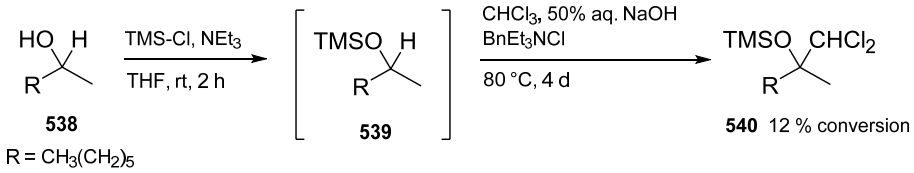


Scheme 176. Observed double inversion of phenyl substrate **532**.

The products of the substitution reaction of aldehyde **537** with azide or cyanide still retained > 98% *e.e*. The absolute configuration of all the compounds was determined by conversion to the known carboxylic acids and comparison of optical rotations.

3.4.2 Synthesis of Dichlorocarbinol Substrates

The stereospecific synthesis of dichlorocarbinols (Scheme 174) seemed desirable to us, since the corresponding racemic substrates ought to be readily synthesised using the well-established LDA/CH_2Cl_2 method. Therefore, we first attempted the carbene insertion reaction reported by Masaki *et al.*, using racemic 2-octanol. Unfortunately, the highest conversion achieved was 12%, over a period of four days at 80 °C using benzyltriethylammonium chloride as the phase transfer catalyst (Scheme 177). This was despite the report claiming an overall yield (after TMS deprotection) of 39% after 18 hours. Alternative phase transfer catalysts tetra-*n*-butylammonium chloride and cetyltrimethylammonium chloride gave even lower conversions.



Scheme 177. Attempted synthesis of dichlorocarbinols by carbene insertion.

Despite this, dichloromethyllithium readily added to a range of general ketones at -78 °C, in moderate to good yields (Figure 27). LDA was chosen as the base as there was little difference when lithium dicyclohexylamide was employed, and LDA is generally used more in organic synthesis. The use of less basic amide base LiHMDS gave poor conversion as expected, due to the decreased acidity of dichloromethane.

It was found that by washing the organic layer several times with pH 2 buffer during the work up all traces of diisopropylamine could be removed. In some cases this allowed the dichlorocarbinol to be used without any further purification, which represents an improvement on the original protocol. A low temperature was vital because at higher reaction temperatures (*e.g.* 0 °C) the LDA began to degrade, resulting in a lower yield.

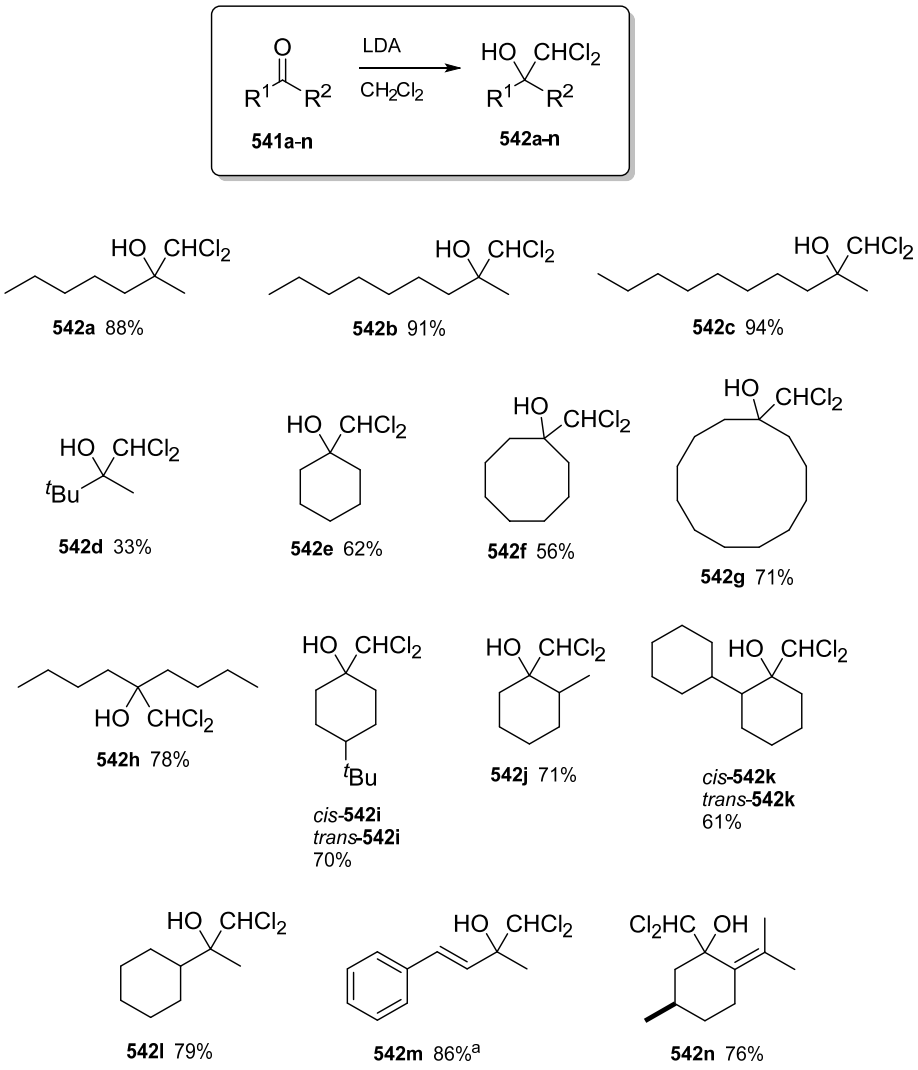


Figure 27. Synthesis of dichlorocarbinols. Reagents and conditions: LDA (2.0 equiv.), CH_2Cl_2, -78 °C, 0.5 h. Yields shown for **542i-k** and **542n** are the combined yield of both diastereoisomers. [a] Crude yield.

Linear, unbranched alkyl ketones (**541a-c**) gave good yields of the dichloromethyl adduct. The branched substrates **541h** and **541l** gave slightly lower yields, with the *tert*-butyl substrate **541d** significantly lower yielding, presumably due to steric hindrance. The cyclic dichlorocarbinols **542e-g** were obtained in similar yields to the trichloromethylation reaction. Compound **542i** was obtained as a 1.6:1 ratio of diastereoisomers, which were readily separated by column chromatography (Figure 28).

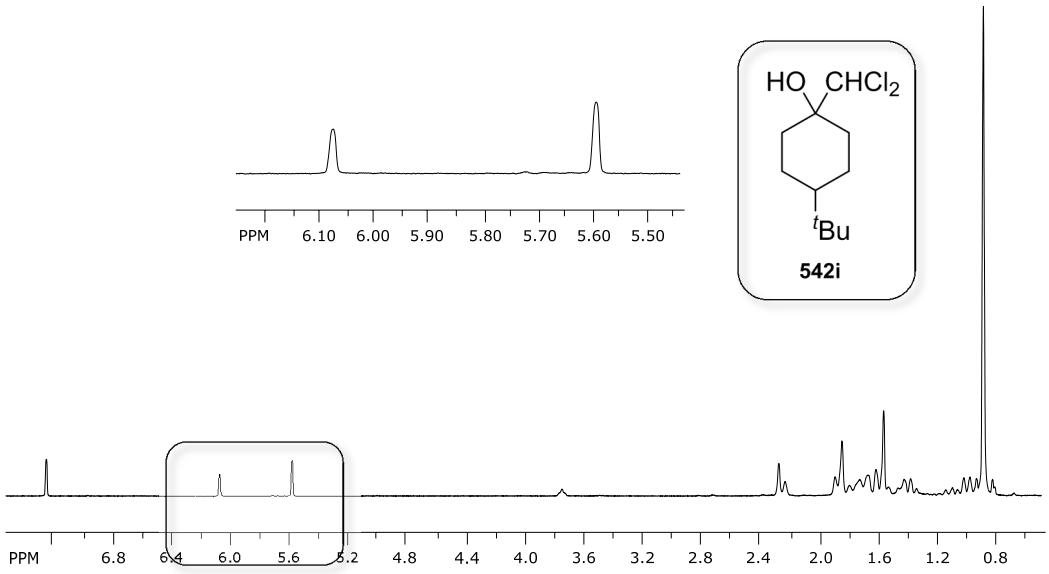


Figure 28. ^{1}H NMR spectrum obtained from crude mixture of **542i**. Inset: $CHCl_2$ peaks used to determine diastereomeric ratio.

Compound **542j** was obtained as an increased 5.8:1 ratio of diastereoisomers (Figure 29), although these were inseparable by column chromatography. The greater selectivity is due to the proximity of the methyl substituent. The bulkier cyclohexyl group provided an even higher selectivity of 11:1 (**542k**, Figure 30), and the diastereoisomers were separable by column chromatography.

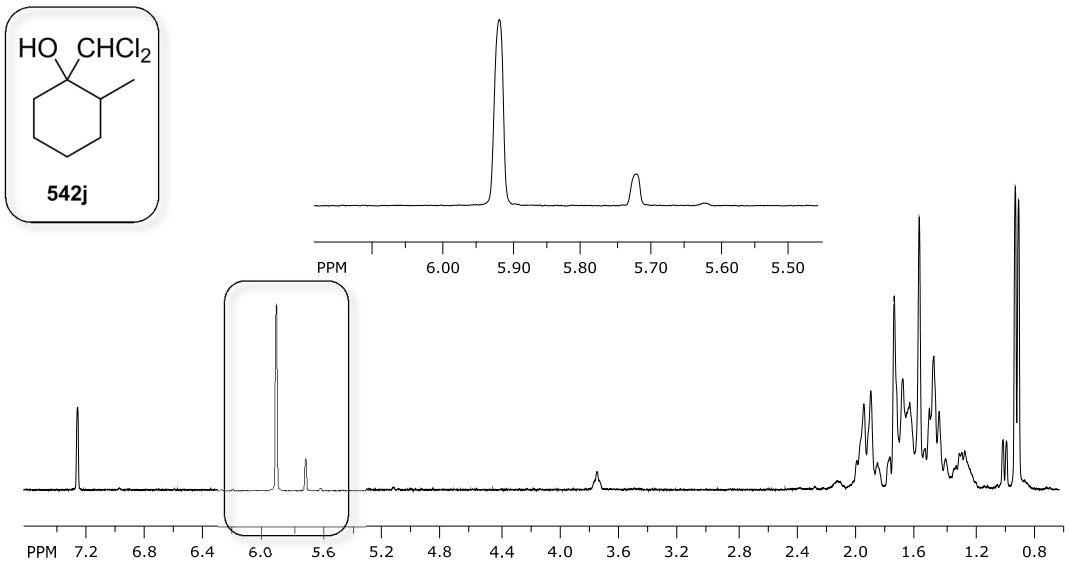


Figure 29. ^{1}H NMR spectrum obtained from crude mixture of **542j**. Inset: $CHCl_2$ peaks used to determine diastereomeric ratio.

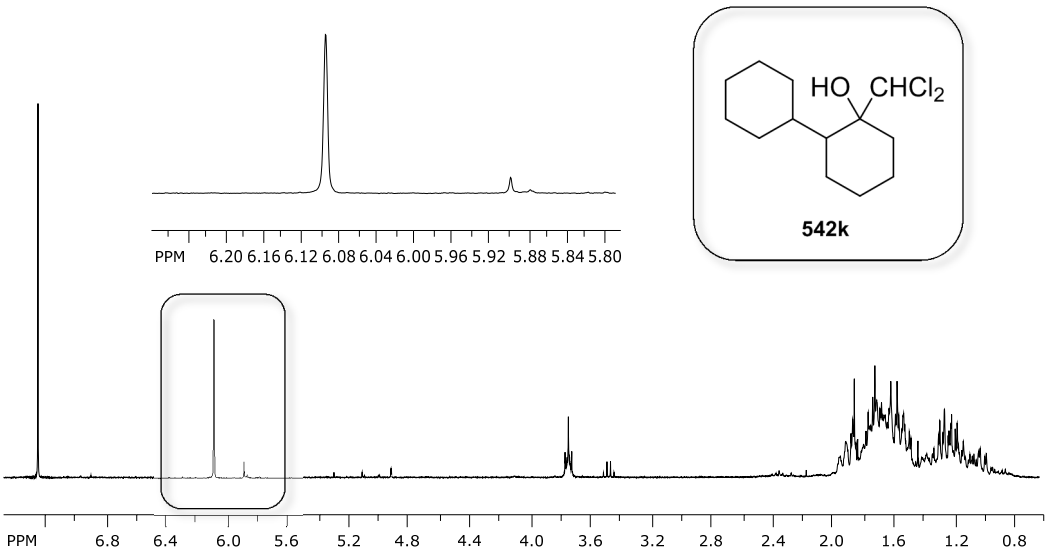


Figure 30. ^{1}H NMR spectrum obtained from crude mixture of **542k**. Inset: $CHCl_2$ peaks used to determine diastereomeric ratio.

The reaction of dichloromethyllithium with (*R*)-pulegone resulted in a selectivity of 13.3:1 (Figure 31), which was the highest observed. These diastereoisomers were also readily separable by column chromatography. The reaction with ketone **541m** did not reach full conversion even using extended reaction times. In addition, the product appeared to degrade on silica gel to the ketone starting material, so it was not tested as

a substrate in the reductive Jocic reaction. An attempted reaction using (*S*)-camphor failed to give a satisfactory yield of dichlorocarbinol under the optimised conditions.

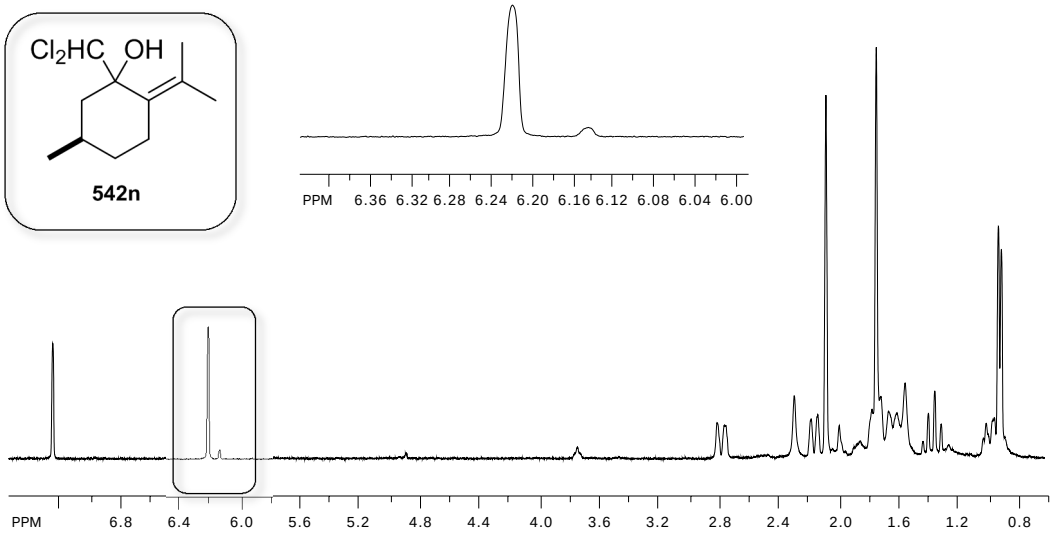


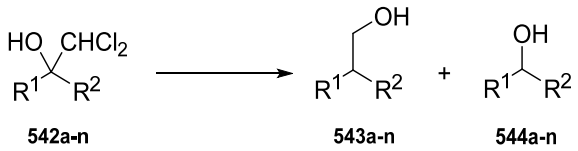
Figure 31. ^{1}H NMR spectrum obtained from crude mixture of **542n**. Inset: $CHCl_2$ peaks used to measure diastereomeric ratio

3.4.3 Jocic Reaction using Hydride Nucleophile

With dichlorocarbinols **542a**-**n** in hand, we then looked to subject them to the same reduction conditions previously developed (section **3.3.2**) and in doing so make some comparison to the use of trichlorocarbinol analogues.

3.4.4 Results

Table 34 shows our results. The linear, alkyl substrates **b** and **c** gave the best results in terms of yield, with minimal secondary alcohol **544** being identified by inspection of the crude ^{1}H NMR spectrum (Figure 32). The lower isolated yield of compound **543a** may be due to its volatility. All three entries represent an improvement on the trichloro- analogues in both isolated yield and the ratio of **543**:**544**. Dichlorocarbinol **542d** failed to undergo the expected reaction, and no identifiable products were observed. This is likely due to the large steric hindrance of the *tert*-butyl group.



entry	ratio 543:544[a]	543 yield (%)	entry	ratio 543:544[a]	543 yield (%)
a	96:4	30	***cis*-i**	100:0	61
b	100:0	75	***trans*-i**	100:0	28
c	100:0	66	**j**	100:0	59
d	-	-[b]	**k**[d]	98:2	39
e	100:0	31	**l**	100:0	46
f	100:0	91[c]	**n**	-	-[b]
g	94:6	56			
h	100:0	65			

Table 34. Reactions and conditions: $LiBH_4$ (4.0 equiv.), NaOH (3.0 equiv.), IPA, rt, 16 h. [a] Ratio determined by examination of the crude ^1H NMR spectrum. [b] Neither product **543** or **544** was observed in the crude mixture. [c] Crude yield: product **543** could not be isolated cleanly. [d] Major diastereomer was used as the substrate as the minor diastereoisomer was inseparable from impurities.

Compound **543e** was isolated in a lower yield, although no trace of side product **544e** was observed. The medium-sized and large rings (entries **f** and **g**) were less suitable substrates, behaviour which was observed for the trichloro-analogues. The reaction with dichlorocarbinol **542f**, although yielding no trace of secondary alcohol side product, gave an alkene side product not observed in any other entries. The proposed mechanistic justification for this will be discussed in section **3.4.5**. The reaction with dichlorocarbinol **542g** showed the lowest **543**:**544** ratio of all the entries, although it still represents a seven-fold improvement over the trichloro- analogue. Notably, the corresponding trichlorocarbinol for entry **h** gave the secondary alcohol in almost a 1:1 ratio. The reactions with single diastereoisomers (*cis*-**542i**, *trans*-**542i**, **542k**) and a mixture of diastereoisomers (**542j**) will be discussed more fully in section **3.4.6**.

Dichlorocarbinol **542l** gave a moderate yield of the desired primary alcohol, with none of the secondary alcohol being observed. The reaction with **542n** yielded none of the desired product, although peaks consistent with S_N2' addition of hydride to the alkene were observed in ^1H NMR spectrum of the crude mixture.

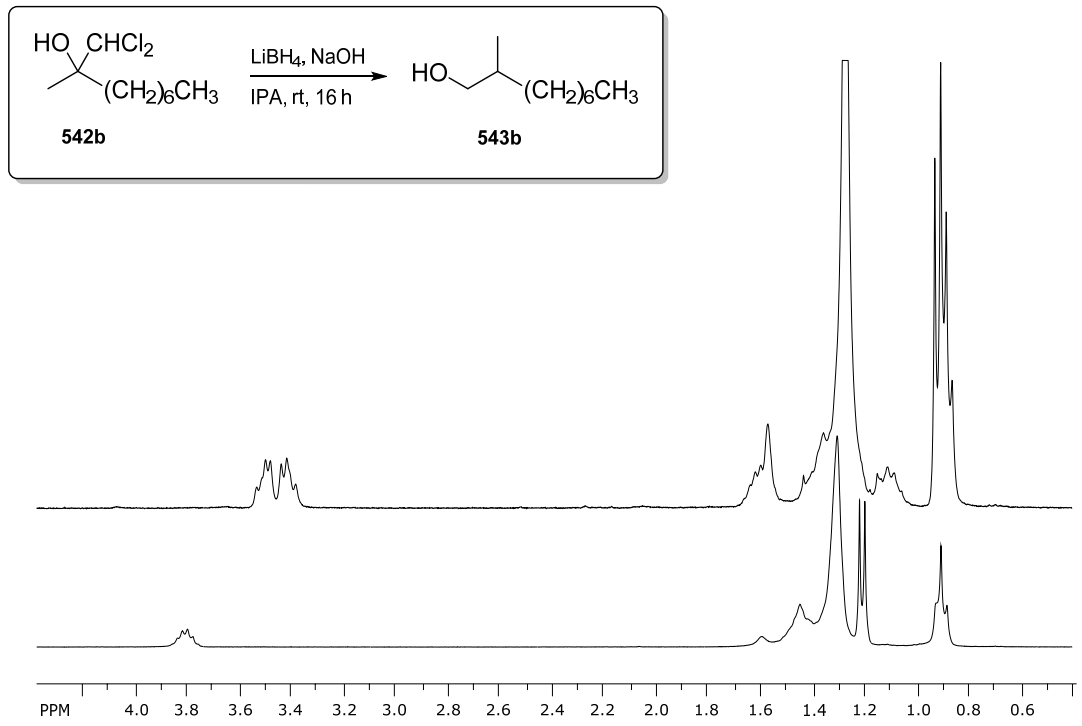
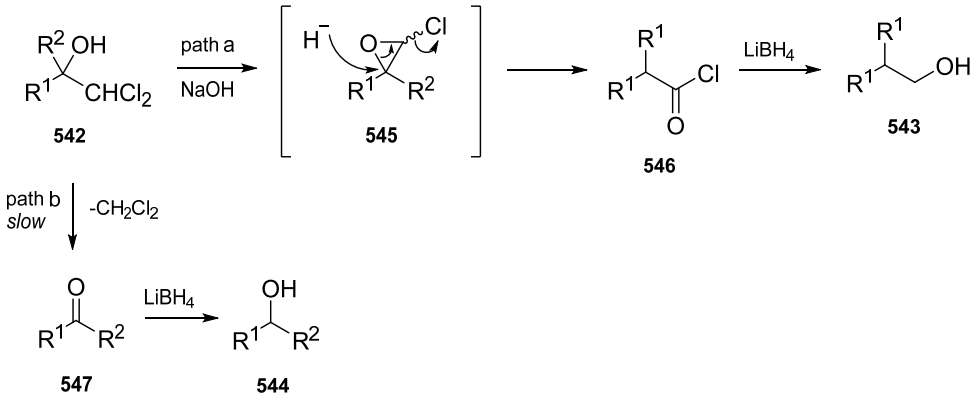


Figure 32. Top ^1H NMR spectrum: obtained from the crude mixture of **543b**. Bottom ^1H NMR spectrum: 2-nonanol.

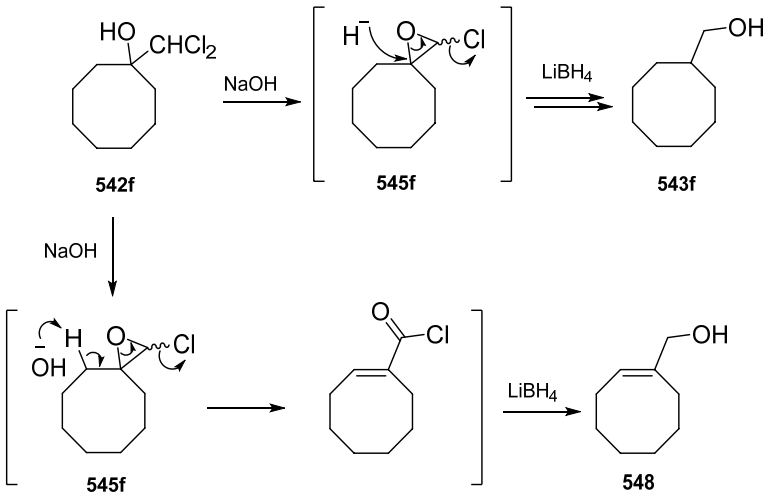
3.4.5 Mechanism Considerations

The potential mechanism by which the secondary alcohol **544** is formed is shown in scheme 178. It is clear from our results that the elimination of CH_2Cl_2 from compound **542** to form the ketone **547** (path b) must be slower than the corresponding elimination of $CHCl_3$. This would be expected due to the increased acidity of $CHCl_3$ compared to CH_2Cl_2. For many of the substrates reaction pathway b became negligible.



Scheme 178. Formation of alcohols **543** and **544**.

From the reaction of dichlorocarbinol **542f** the allylic alcohol **548** was formed, and it was inseparable from the desired primary alcohol **543f** (Scheme 179).



Scheme 179. Possible mechanism for the formation of an allylic alcohol side product.

It was interesting to note that in none of the experiments run was any ring opening at the non-chlorinated carbon of the intermediate chloroepoxide observed. For the analogous dichloroepoxide this might be expected mainly on the grounds of electronics, since the epoxide ring opening likely involves a "late" S_N2 transition state. Lengthening of the C-O bond causes a build-up of positive charge on the carbon atom, and the chlorine atoms will raise the energy of **TS2** relative to **TS1** (Figure 33).

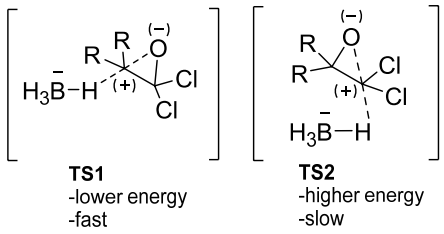


Figure 33. Illustration of possible transition states in the ring opening of *gem*-dichloroepoxides.

Evidently, one chlorine atom is enough to sufficiently raise the energy barrier for this pathway to still be negligible. Comparison of the ^{1}H NMR spectra of the independently synthesised tertiary alcohol **549** with that of the crude reaction mixture obtained from dichlorocarbinol **542c** illustrates this (Figure 34). Tertiary alcohol **549** was synthesised by addition of MeMgBr to 2-decanone (Scheme 180).

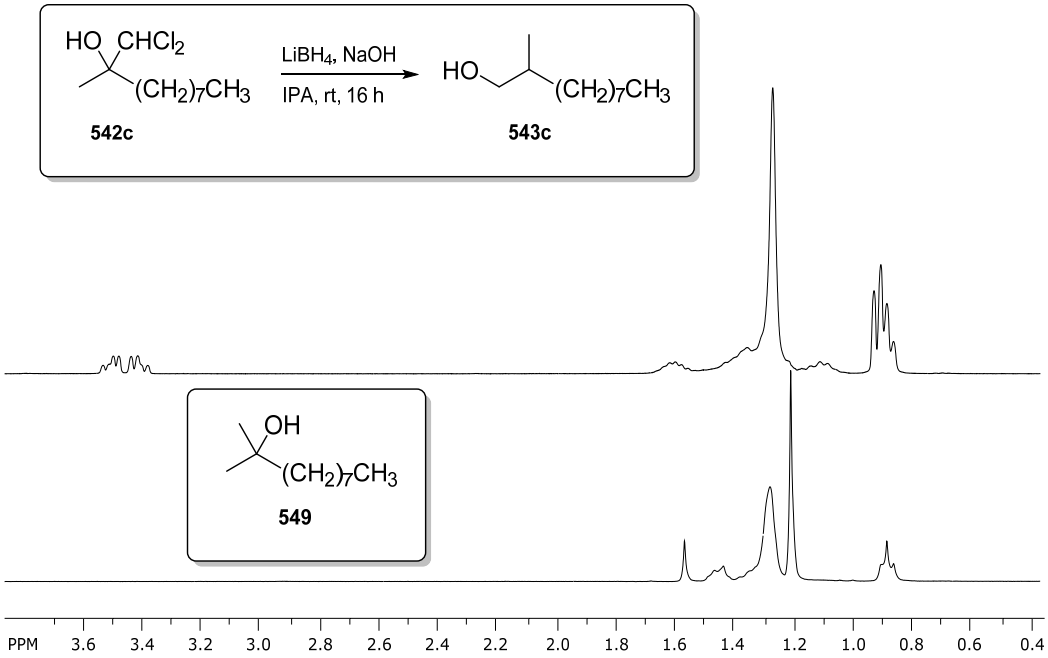
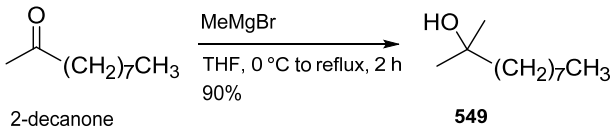
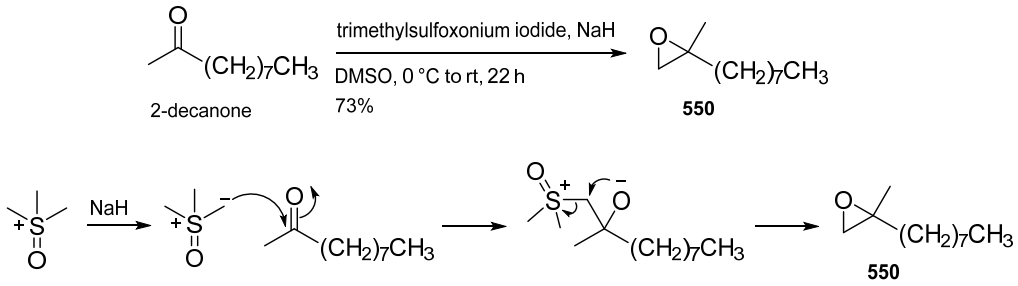


Figure 34. Top ^{1}H NMR spectrum: crude reaction mixture of **543c**. Bottom ^{1}H NMR spectrum: tertiary alcohol **549**.

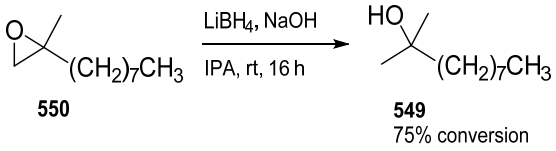


Scheme 180. Synthesis of tertiary alcohol **549**.

As can be seen in figure 34, no tertiary alcohol was observed in the Jocic reaction of dichlorocarbinol **542c**, corresponding to complete regioselectivity for the non-chlorinated carbon. Non-chlorinated epoxides will generally react with a hydride nucleophile at the less hindered end. For example, epoxide **550** (synthesised independently using a Corey-Chaykovsky reaction,[460] scheme 181) was subjected to our reduction conditions (Scheme 182) and the crude ^{1}H NMR spectrum was examined (Figure 35).



Scheme 181. Synthesis of epoxide **550** using a Corey-Chaykovsky reaction.



Scheme 182. Reaction of epoxide **550** with $LiBH_4$ and NaOH.

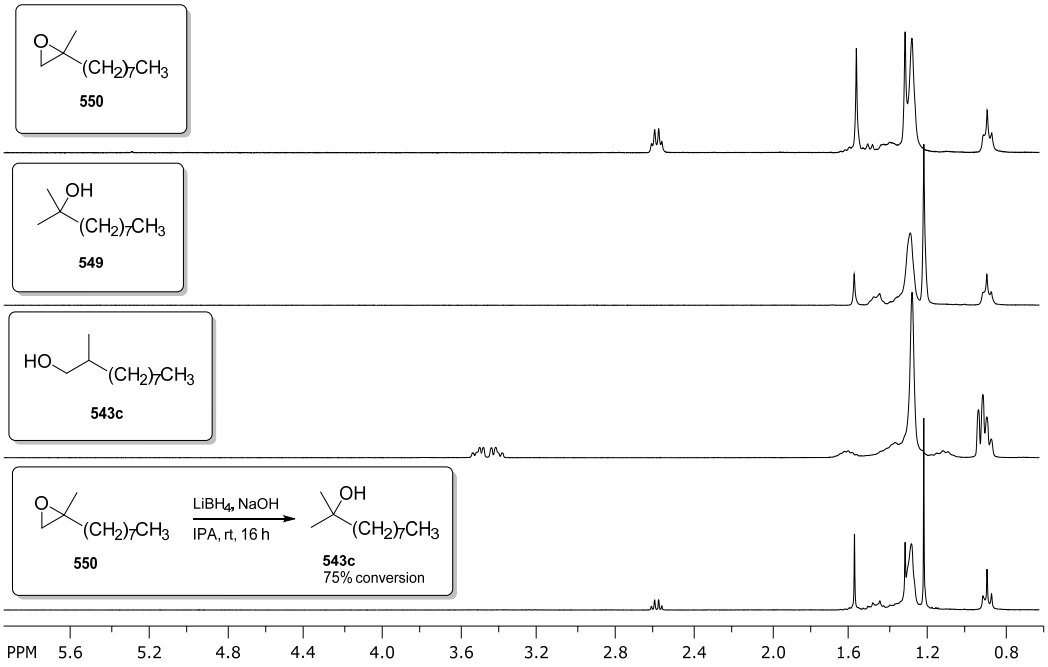


Figure 35. ^{1}H NMR spectra from top to bottom: starting material epoxide **550**; tertiary alcohol **549**; primary alcohol **543c**; crude reaction mixture of epoxide **550** subjected to our Jocic reduction conditions.

As can be seen from the ^{1}H NMR spectra, under our Jocic reaction conditions the epoxide **550** undergoes ring opening at the less hindered end, and the reaction only reached ~75% conversion. No trace of the primary alcohol resulting from attack at the more hindered end of the epoxide was observed.

3.4.6 Stereochemistry

The separation by column chromatography of the *cis* and *trans* diastereoisomers of dichlorocarbinol **542i** allowed us to gain some insight into the stereochemistry of the Jocic reaction under these conditions. Therefore, each single isolated diastereoisomer and a mixture of the two diastereoisomers was reacted under the same conditions and the reaction mixtures were analysed by ^{1}H NMR spectroscopy (Figure 36).

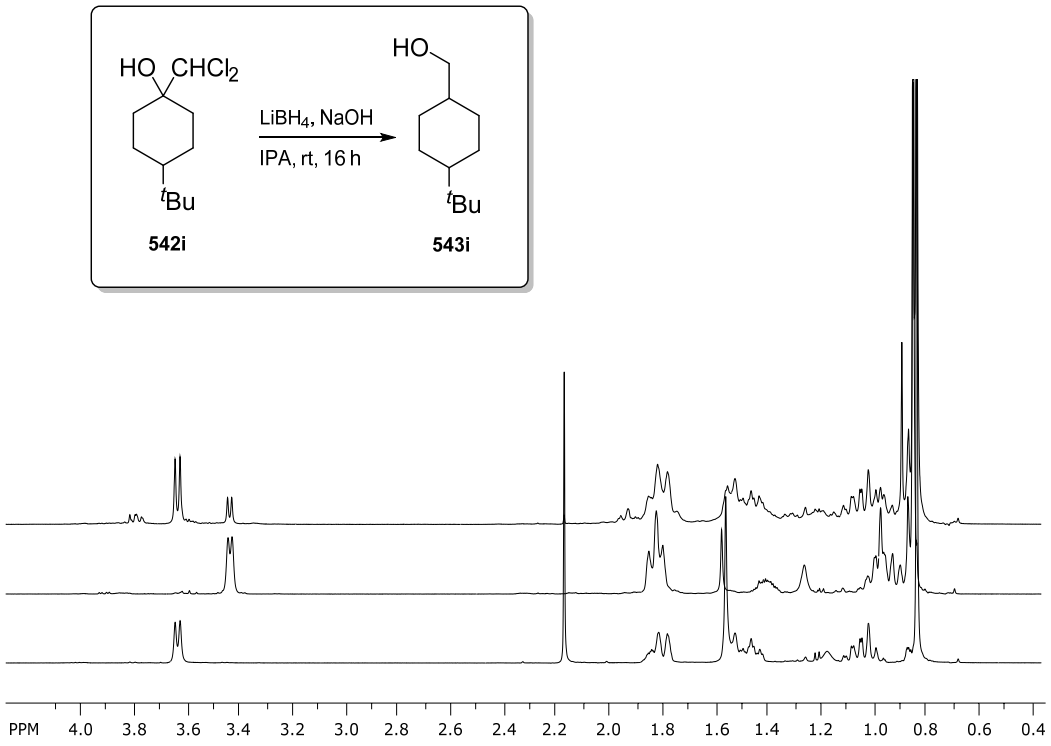


Figure 36. Top ^{1}H NMR spectrum: obtained from the reaction of a mixture of both **542i** diastereoisomers. Middle ^{1}H NMR spectrum: obtained from the reaction of the more polar diastereoisomer of **542i**. Bottom ^{1}H NMR spectrum: obtained from the reaction of the less polar diastereoisomer of **542i**.

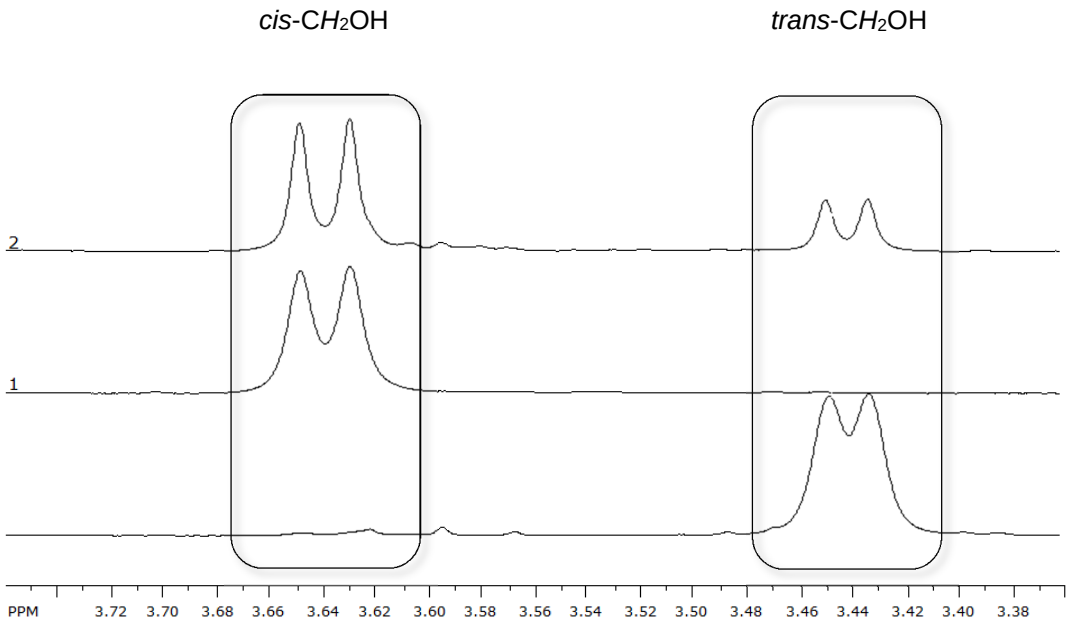
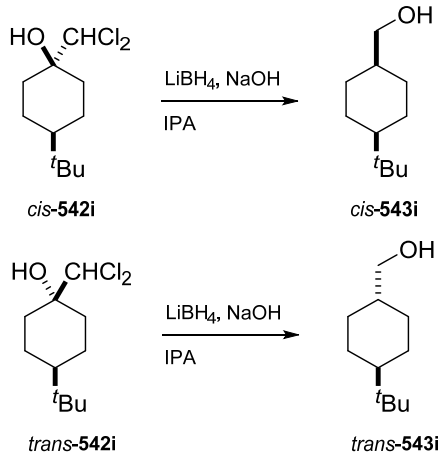


Figure 37. Magnification of α-CH peaks.

Note that the relative configuration was not known prior to carrying out the Jocic reaction. Each diastereoisomer was crystalline but unfortunately we were not able to grow suitable crystals for X-ray crystallography.

Although the relative stereochemistry of each diastereoisomer of **542i** was not known beforehand, the Jocic reaction is known to go with inversion. The *cis*- and *trans*-alcohols **543i** were known in the literature,[461, 462] so by identifying the relative stereochemistry of the primary alcohol products we were able to tentatively assign the stereochemistry of the starting materials (Scheme 183). In this way, the less polar diastereoisomer of **542i** was assigned as *cis*, and the more polar diasteroisomer was assigned as *trans*. The ^{1}H NMR spectra established that none of the opposite diastereoisomer was present in each reaction. This indicates that the reaction is highly stereospecific, and that no epimerisation of the C-1 stereocentre is taking place during the reaction.



Scheme 183. Inversion of configuration at the C-1 centre during the Jocic reaction.

Compound **542k** was reacted as the major diastereoisomer only, since the minor diastereoisomer could not be isolated cleanly. NMR data for the resulting 2-cyclohexylcyclohexyl methanol product **543k** was not available, which made analysis

of the reaction stereochemistry difficult, although there appeared to be only a single diastereoisomer with a negligible presence of the secondary alcohol (Figure 38).

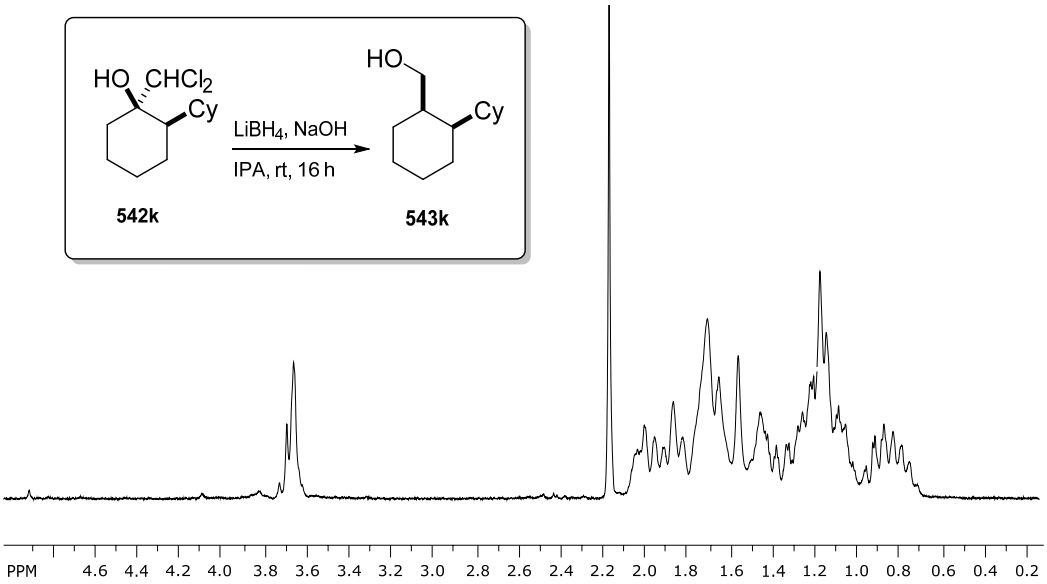


Figure 38. ^{1}H NMR spectrum of the crude mixture from the Jocic reaction of dichlorocarbinol **542k**.

However, the melting point (56-57 °C) agreed reasonably well with the literature for the *cis* diastereoisomer (lit. 62-63 °C[463]). The melting point of the *trans* diastereoisomer was reported to be 160-162 °C from the same reference. Thus, the major diastereoisomer of dichlorocarbinol **542k** can tentatively be assigned as *cis*, which is as expected due to attack of dichloromethyllithium at the less hindered face of the cyclohexanone ring.

Compound **542j** was reacted as an inseparable 5.8:1 mixture of diastereoisomers. The ^{1}H NMR spectrum of the crude mixture (Figure 39) suggested an increased 33:1 ratio of diastereoisomers, with the major isomer agreeing with literature data for the *cis* configured alcohol **543j**.[464] This suggests a *cis*-configuration for the major diastereoisomer of the dichlorocarbinol **542j**. The diastereoisomers of the product alcohol **543j** were separable by column chromatography.

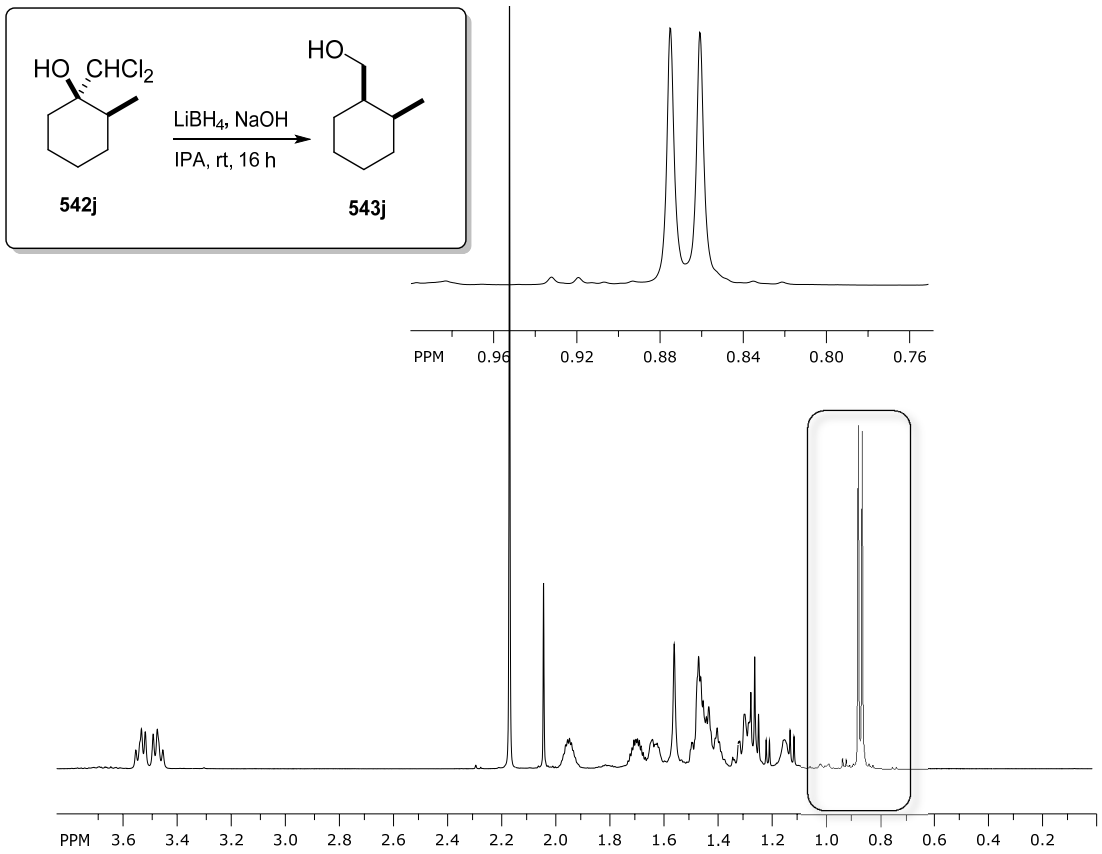
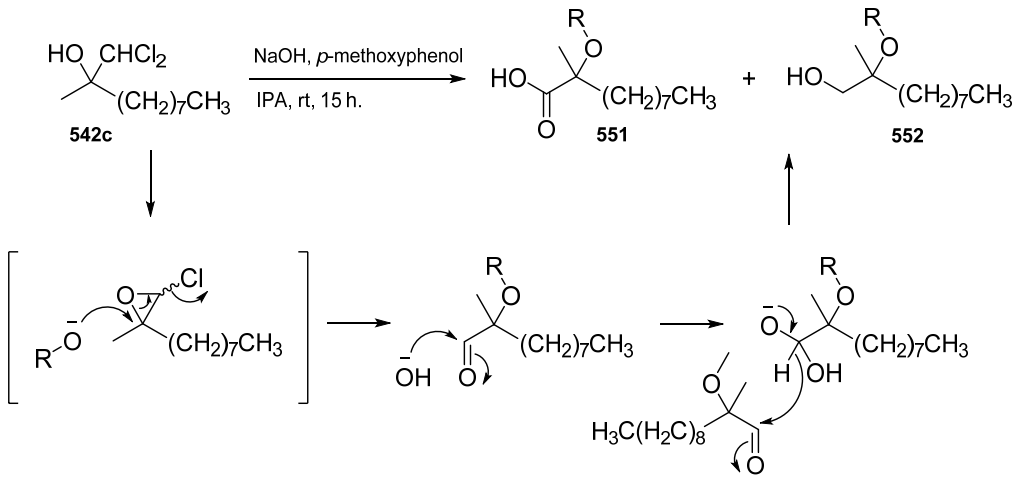


Figure 39. ^{1}H NMR spectrum of the crude mixture from the Jocic reaction with dichlorocarbinol **542j**. Inset: C*H*$_3$CH doublets used to determine the diastereomeric ratio.

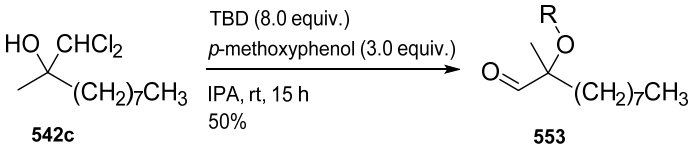
3.5 Other Nucleophiles

Phenoxide had previously been shown by Fechtel *et al*. to participate in a Jocic reaction with secondary dichlorocarbinols to yield α-substituted aldehydes. However, we found that treatment of the tertiary dichlorocarbinol **542c** with *p*-methoxyphenol and NaOH yielded a mixture of products **551** and **552**, from the Cannizzaro reaction of the α-substituted aldehyde (Scheme 184).



Scheme 184. Attempted Jocic reaction with a phenoxide nucleophile. R = *p*-$OCH_3C_6H_4$.

We imagined that the use of a strong, non-nucleophilic organic base would prevent the aldehyde product from undergoing a Cannizzaro reaction. Accordingly, treatment of dichlorocarbinol **542c** with triazabicyclodecene (TBD) and *p*-methoxyphenol in IPA solvent yielded the α-disubstituted aldehyde **553** smoothly (Scheme 185).



Scheme 185. Synthesis of α-aryloxyaldehyde **553**. R = *p*-$OCH_3C_6H_4$.

3.6 Conclusions and Future Work

The Jocic reaction with a hydride nucleophile, as first described by Snowden *et al*. for secondary trichlorocarbinols, was applied to tertiary trichlorocarbinol substrates for the first time. With tertiary trichlorocarbinols, elimination of $CHCl_3$ was observed which ultimately led to the formation of significant quantities of a secondary alcohol side product. This side product was often inseparable from the desired primary alcohol, making purification difficult. In spite of this, the reaction was shown to be highly stereospecific when an enantiomerically pure, tertiary trichlorocarbinol was used as the substrate. This reaction ultimately led to the stereoselective synthesis of (*R*)-dihydrocitronellol and (3*R*,7*R*)-hexahydrofarnesol.

The use of dichlorocarbinols, synthesised by straightforward addition of lithiated dichloromethane to ketones, greatly improved the Jocic procedure and little to no side products were observed in this reaction. Several cyclohexanones containing a stereogenic centre could be dichloromethylated with good diastereoselectivity. Moreover, the addition of hydride to these substrates was shown to be both highly regioselective and highly stereospecific. No epimerisation of the newly generated stereogenic centre was observed in the reaction.

Clearly, a more comprehensive study of the reaction using enantiomerically pure substrates would be desirable. Currently no methods exist for the enantioselective synthesis of tertiary dichlorocarbinols, bar the carbene insertion reported by Masaki *et al*.,[458, 459] which in our hands failed for alkyl secondary alcohols. For aryl substrates more promising results have been obtained by another member of the group.

One additional nucleophile (phenoxide) was used in the Jocic reaction (Scheme 185). Other nucleophiles could be explored – for example *N*-based nucleophiles or *S*-based

nucelophiles. The use of bidentate nucleophiles could generate substituted cyclic structures as has been shown by Perryman *et al*.[361]

Sugar-derived ketones have been shown to provide excellent selectivity for the addition of both trichloromethide and dichloromethide.[366, 370-372, 455-457] Subsequent Jocic reactions on these stereochemically pure compounds has largely been restricted to the use of azide nucleophiles. We envisage that the use of our developed conditions could provide a highly stereospecific route to one-carbon homologated sugar compounds. This approach would be especially versatile for glucose since the hydroxyls at the C-2, C-3, C-4 and C-6 positions can be selectively protected.[465]

3.7 Experimental Section

All the reagents and solvents used were purchased from Sigma-Aldrich, Alfa-Aesar, TCI, Fluorochem or Acros Organics and were used as received unless stated otherwise. Solvents were dried over 3Å or 4Å molecular sieves when necessary.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVII-700 MHz, AVIII HD-500 MHz, AVIII HD-400 MHz, AVIII HD-300 MHz or AV-300 MHz Fourier transform spectrometer, at room temperature unless stated otherwise. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane. Solvents were used as an internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, $(CD_3)_2SO$ 2.50 ppm, D_2O 4.79 ppm; δ_C: $CDCl_3$ 77.1 ppm, CD_3OD 49.0 ppm, $(CD_3)_2SO$ 39.5 ppm). Coupling constants (*J*) are quoted in Hertz (Hz) and rounded to the nearest 0.5 Hz. Abbreviations used in the descriptions of spectra are as follows; s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded with proton decoupling and the spectra were assigned on the basis of COSY, PENDANT, HSQC and HMBC experiments.

Infrared spectra were recorded on a Bruker ALPHA platinum ATR spectrometer using OPUS software and are quoted in wavenumbers (cm^{-1}).

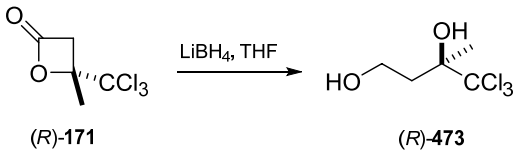
HPLC data were obtained on a Varian Prostar 335LC detector using a Chiralcel Daicel AD-H column (4.6 mm x 250 mm), with a solvent system of *n*-hexane:2-propanol.

Melting points for solid crystalline products were determined using a Stuart Scientific SMP10 Digital Melting Point Apparatus, with a range given in °C and rounded to the nearest degree. The melting points are uncorrected.

Gas chromatography mass spectrometry (GC/MS) data was recorded on a Varian 3800-4000 GC-MS machine.

Thin Layer Chromatography (TLC) was carried out using silica coated (0.25 mm) alumina plates, and the plates were visualised using UV light or by staining with $KMnO_4$.

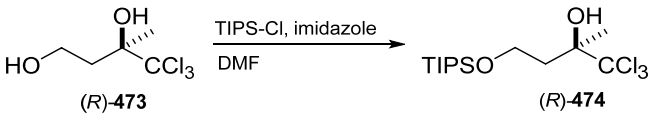
(*R*)-4,4,4-Trichloro-3-methylbutane-1,3-diol 473



(*R*)-**171** (*R*)-**473**

To a solution of (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one **171** (0.221 g, 1.02 mmol) in dry THF (5 mL) was added $LiBH_4$ (66.0 mg, 3.00 mmol) at 0 °C under nitrogen. The mixture was stirred at this temperature until the reaction was complete by TLC, then quenched with water and filtered through celite with EtOAc. The solvent was removed *in vacuo* to yield product as a white solid (0.204 g, 99%). The compound was used without further purification. ν (cm^{-1}); 3357 (br, O-H stretch), 1129 (C-O stretch), 788 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.07-3.88 (2H, m, C*H*$_2$OH), 3.49 (1H, s, OH), 2.47 (1H, dddd, *J* 15, 9.5, 4.5, 0.5, C*H*HCH$_2$OH), 2.16 (1H, t, *J* 5, OH), 2.09 (1H, ddd, *J* 15, 4.5, 3.5, CH*H*CH$_2$OH), 1.68 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.0 (CCl_3), 83.5 (*C*(CH_3)), 59.8 (CH_2OH), 37.1 (*C*H$_2$CH$_2$OH), 22.6 (CH_3); m.p = 64-65 °C; $[\alpha]_D^{25}$ -7.5 (*c* 1, $CHCl_3$).

(*R*)-1,1,1-Trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol 474

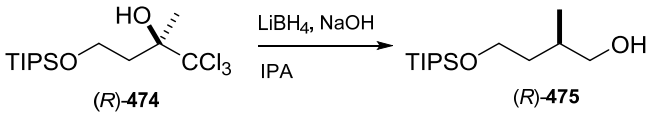


(*R*)-**473** (*R*)-**474**

To a solution of (*R*)-4,4,4-trichloro-3-methylbutane-1,3-diol **473** (0.204 g, 0.990 mmol) in DMF (2 mL) was added imidazole (0.135 g, 1.98 mmol) and triisopropylsilyl chloride (0.250 mL, 1.19 mmol) under nitrogen, and the solution was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq.) and

extracted with CH_2Cl_2. The combined organic fractions were washed with pH 2 buffer, water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (40:1 petroleum ether/Et_2O) to yield product as a colourless oil (0.212 g, 59%). ν (cm^{-1}); 3434 (br, O-H stretch), 2925 (C-H stretch), 1106 (C-O stretch), 1085 (Si-O stretch), 797 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (1H, s, OH), 4.14-4.04 (2H, m, C*H*$_2$OSi), 2.48 (1H, ddd, *J* 14.5, 10, 4.5, C*H*HCH$_2$OSi), 2.01 (1H, ddd, *J* 14.5, 4, 3, CH*H*CH$_2$OSi), 1.66 (3H, s, OC(*C*H$_3$)), 1.19-1.06 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.2 (CCl_3), 83.0 (O*C*(CH$_3$)), 60.9 (CH_2OSi), 37.1 (*C*H$_2$CH$_2$OSi), 27.8 (OC(*C*H$_3$)), 18.1 (SiCH*C*H$_3$), 11.8 (Si*C*HCH$_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{29}{}^{35}Cl_3NaO_2Si$ $[M+Na]^+$ 385.0895, found 385.0892; $[\alpha]_D{}^{25}$ -20.7 (*c* 1.98, $CHCl_3$).

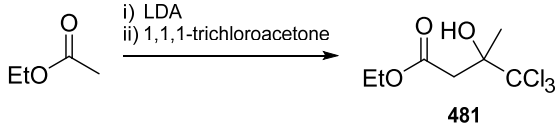
(*R*)-2-Methyl-4-((triisopropylsilyl)oxy)butan-1-ol 475



To a solution of (*R*)-1,1,1-trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol **474** (0.210 g, 0.580 mmol) in dry propan-2-ol (2 mL) was added $LiBH_4$ (51.0 mg, 2.32 mmol) and freshly powdered NaOH (70.0 mg, 1.74 mmol) under nitrogen. The mixture was stirred at 40 °C until the reaction was complete by TLC (17 h), when it was quenched with saturated NH_4Cl (aq.) (5 mL). The aqueous phase was saturated with solid NaCl and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (9:1 petroleum ether/EtOAc) to yield product as a colourless oil (97.0 mg, 64%). ν (cm^{-1}); 3342 (br, O-H stretch), 2941 (C-H stretch), 1095 (Si-O stretch), 678 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88-3.81 (1H, m, C*H*HOSi), 3.78-3.71 (1H, m, CH*H*OSi), 3.57-3.49 (1H, m, C*H*HOH), 3.43 (1H, ddd,

J 16, 5, 2, CH*H*OH), 3.09 (1H, dd, *J* 7.5, 5.5, OH), 1.88-1.78 (1H, m, C*H*CH_3), 1.60-1.55 (2H, m, C*H*$_2$$CH_2$OSi), 1.17-1.04 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.92 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.4 (CH_2OH), 62.2 (CH_2OSi), 37.9 (*C*H_2CH_2OSi), 34.8 (*C*HCH_3), 18.1 (SiCH*C*H_3), 17.6 (CH*C*H_3), 12.0 (Si*C*HCH_3); LRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{32}NaO_2Si$ $[M+Na]^+$ 283.5, found 283.2; $[\alpha]_D^{20}$ +3.4 (*c* 0.36, $CHCl_3$). ^{1}H and ^{13}C NMR data are consistent with the previously reported data for the (*S*) isomer.[295]

Ethyl 4,4,4-trichloro-3-hydroxy-3-methylbutanoate 481

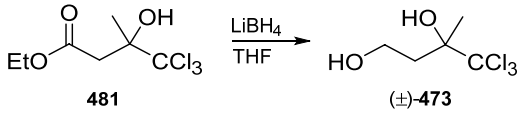


481

To a solution of diisopropylamine (0.78 mL, 5.5 mmol) in dry THF (5 mL) was added *n*-BuLi (2.0 mL, 2.5M, 5.0 mmol), at 0 °C under nitrogen. The solution was then cooled to -78 °C and stirred for one hour, after which time EtOAc (0.49 mL, 5.0 mmol) was added. The solution was stirred for a further one hour at -78 °C and 1,1,1-trichloroacetone (0.67 mL, 6.0 mmol) was added. The reaction was quenched with saturated NH_4Cl (aq.) after 10 minutes and poured into water. The aqueous layer was extracted with Et_2O and the combined organic fractions were washed with water and brine. After drying over Na_2SO_4 the solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1 petroleum ether/EtOAc), to yield product as a yellow oil (0.820 g, 66%). ν (cm^{-1}); 3466 (br, O-H stretch), 1711 (C=O stretch), 1204 and 1026 (C-O stretch), 789 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.65 (1H, s, OH), 4.23 (2H, q, *J* 7, C*H*$_2$$CH_3$), 3.14 (1H, d, *J* 15.5, C*H*HCO), 2.86 (1H, d, *J* 15.5, CH*H*CO), 1.71 (3H, s, OC(CH_3)), 1.31 (3H, t, *J* 7, CH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8 (CO), 107.3 (CCl_3), 81.2 (O*C*(CH_3)), 61.6 (CH_2O), 40.2

(*C*H_2CO), 23.5 (OC(*C*H_3)), 14.1 (CH_2*C*H_3); HRMS (ESI) *m*/*z*: calcd. for $C_7H_{11}{}^{35}Cl_3NaO_3$ $[M+Na]^+$ 270.9666, found 270.9674.

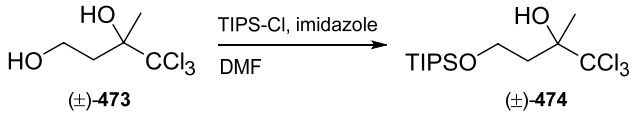
4,4,4-Trichloro-3-methylbutane-1,3-diol (±)-473



481 (±)-**473**

To a solution of ethyl 4,4,4-trichloro-3-hydroxy-3-methylbutanoate **481** (0.296 g, 1.19 mmol) in dry THF (5 mL) was added $LiBH_4$ (52.0 mg, 2.38 mmol) under nitrogen at 0 °C. The mixture was stirred at this temperature until the reaction was complete by TLC (four hours). The reaction was quenched with water (2 mL) and saturated $NaHCO_3$ (aq.) (3 mL), filtered through celite and the solvent was removed *in vacuo*. The residue was purified by column chromatography (6:4 petroleum ether/EtOAc) to yield product as a white solid (0.177 g, 72%). ν (cm^{-1}); 3358 (br, O-H stretch), 1128 (C-O stretch), 793 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06-3.94 (2H, m, C*H*$_2$OH), 3.48 (1H, s, OH), 2.47 (1H, dddd, *J* 15, 9.5, 4.5, 0.5, C*H*HCH$_2$OH), 2.15 (1H, dd, *J* 6, 4, OH), 2.09 (1H, dt, *J* 15, 4.5, CH*H*CH$_2$OH), 1.68 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.9 (CCl_3), 83.4 (*C*(CH_3)), 59.7 (CH_2OH), 37.0 (*C*H_2CH$_2$OH), 22.5 (CH_3); m.p = 98-99 °C.

1,1,1-Trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol (±)-474

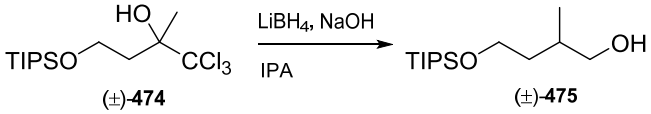


(±)-**473** (±)-**474**

To a solution of 4,4,4-trichloro-3-methylbutane-1,3-diol (±)-**473** (0.222 g, 1.07 mmol) in DMF (2 mL) was added imidazole (0.146 g, 2.15 mmol) and triisopropylsilyl chloride (0.270 mL, 1.28 mmol) under nitrogen, and the solution was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq.) and

extracted with CH_2Cl_2. The combined organic fractions were washed with pH 2 buffer, water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (40:1 petroleum ether/Et_2O) to yield product as a colourless oil (0.272 g, 70%). ν (cm^{-1}); 3443 (br, O-H stretch), 2940 (C-H stretch), 1110 (C-O stretch), 884 (Si-O stretch), 797 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.00 (1H, s, OH), 4.14-4.04 (2H, m, CH_2OSi), 2.47 (1H, ddd, *J* 15, 10, 5, C*H*HCH$_2$OSi), 2.01 (1H, dt, *J* 14.5, 3, CH*H*CH$_2$OSi), 1.66 (3H, s, OC(CH_3)), 1.89-1.01 (21H, m, Si(C*H*(CH_3)$_2$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.2 (CCl_3), 83.0 (C(OH)), 60.9 (CH_2OSi), 37.1 (*C*H$_2$CH$_2$OSi), 22.7 (OC(*C*H$_3$)), 18.1 (SiCH*C*H$_3$), 11.8 (Si*C*HCH$_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{29}{}^{35}Cl_3NaO_2Si$ $[M+Na]^+$ 385.0895, found 385.0893.

2-Methyl-4-((triisopropylsilyl)oxy)butan-1-ol (±)-475

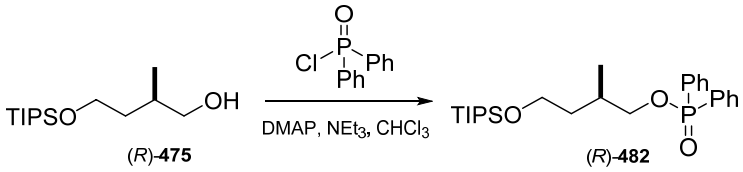


(±)-**474** (±)-**475**

To a solution of 1,1,1-trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol (±)-**474** (0.210 g, 0.580 mmol) in dry propan-2-ol (2 mL) was added $LiBH_4$ (51.0 mg, 2.32 mmol) and freshly powdered NaOH (70.0 mg, 1.74 mmol) under nitrogen. The mixture was stirred at 40 °C until the reaction was complete by TLC (17 h), when it was quenched with saturated NH_4Cl (aq.) (5 mL). The aqueous phase was saturated with solid NaCl and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (9:1 petroleum ether/EtOAc) to yield product as a colourless oil (0.103 g, 56%). %). ν (cm^{-1}); 3327 (br, O-H stretch), 2941 (C-H stretch), 1096 (Si-O stretch), 680 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88-3.81 (1H, m, C*H*HOSi), 3.77-3.70 (1H, m, CH*H*OSi), 3.56-3.49 (1H, m, C*H*HOH), 3.46-3.40 (1H,

m, CH*H*OH), 3.09 (1H, dd, *J* 7.5, 5.5, OH), 1.90-1.77 (1H, m, C*H*CH_3), 1.60-1.55 (2H, m, C*H*$_2$$CH_2$OSi), 1.17-1.03 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.92 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.4 (CH_2OH), 62.2 (CH_2OSi), 37.9 (*C*H_2CH_2OSi), 34.8 (*C*HCH_3), 18.1 (SiCH*C*H_3), 17.6 (CH*C*H_3), 12.0 (Si*C*HCH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{32}NaO_2Si$ $[M+Na]^+$ 283.2064, found 283.2062.

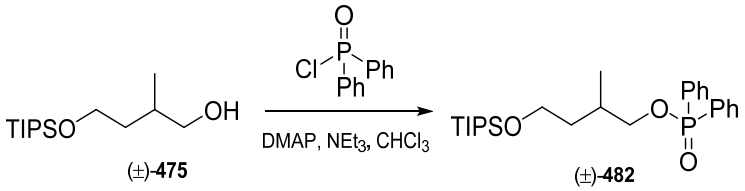
(*R*)-2-Methyl-4-((triisopropylsilyl)oxy)butyl diphenylphosphinate 482



To a solution of (*R*)-2-methyl-4-((triisopropylsilyl)oxy)butan-1-ol **475** (85.0 mg, 0.327 mmol) in dry $CHCl_3$ (3 mL) was added NEt_3 (0.135 mL, 0.981 mmol), DMAP (40.0 mg, 0.327 mmol) and diphenylphosphinic chloride (0.100 mL, 0.490 mmol) under nitrogen. The mixture was stirred at room temperature until complete by TLC, quenched with saturated $NaHCO_3$ (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with saturated $NaHCO_3$ (aq.), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether/EtOAc) to yield product as a colourless oil (0.120 g, 80%, 92% *e.e.*). ν (cm^{-1}); 2940 (C-H stretch), 1430 (P-Ph stretch), 1228 (P=O stretch), 1099 (Si-O stretch), 692 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84-7.77 (4H, m, Ph-H), 7.54-7.49 (2H, m, Ph-H), 7.47-7.41 (4H, m, Ph-H), 3.94-3.81 (2H, m, CH_2OP), 3.77-3.67 (2H, m, CH_2OSi), 2.13-2.02 (1H, m, C*H*CH_3), 1.78-1.69 (1H, m, C*H*HCH_2OSi), 1.46-1.36 (1H, m, CH*H*CH_2OSi), 1.09-0.97 (24H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.2 (2 x Ph-C_{para}), 131.8 (d, *J* 10, 4 x Ph-C_{meta}), 131.8 (d, *J* 137, 2 x Ph-C_{ipso}), 128.6 (d, *J* 13, 4 x Ph-C_{ortho}), 69.6 (d, *J* 6, CH_2OP), 61.2 (CH_2OSi), 36.4 (*C*H_2CH_2OSi), 31.1 (d, *J* 7,

*C*HCH$_3$), 18.2 (SiCH*C*H$_3$), 16.8 (CH*C*H$_3$), 12.1(Si*C*HCH$_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{26}H_{41}NaO_3PSi$ $[M+Na]^+$ 483.2455, found 483.2457; $[\alpha]_D^{25}$ -1.3 (*c* 1.3, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiracel AD-H column, 2-propanol : hexane = 2 : 98, 1 mL/min, 226 nm, (*S*) isomer 32.49 min, (*R*) isomer 36.84 min).

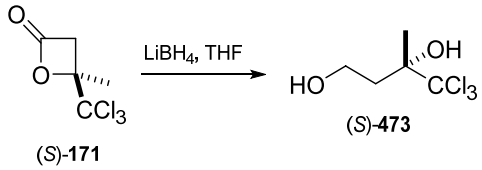
2-Methyl-4-((triisopropylsilyl)oxy)butyl diphenylphosphinate (±)-482



To a solution of 2-methyl-4-((triisopropylsilyl)oxy)butan-1-ol (±)-**475** (90.0 mg, 0.346 mmol) in dry $CHCl_3$ (3 mL) was added NEt_3 (0.140 mL, 1.04 mmol), DMAP (42.0 mg, 0.346 mmol) and diphenyl phosphinic chloride (93.7 µL, 0.490 mmol) under nitrogen. The mixture was stirred at room temperature until complete by TLC, quenched with saturated $NaHCO_3$ (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with saturated $NaHCO_3$ (aq.), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether/EtOAc) to yield product as a colourless oil (0.129 g, 81%). ν (cm^{-1}); 2940 (C-H stretch), 1439 (P-Ph stretch), 1229 (P=O stretch), 1099 (Si-O stretch), 693 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84-7.77 (4H, m, Ph-H), 7.54-7.49 (2H, m, Ph-H), 7.47-7.41 (4H, m, Ph-H), 3.94-3.81 (2H, m, CH_2OP), 3.77-3.68 (2H, m, CH_2OSi), 2.13-2.02 (1H, m, C*H*CH$_3$), 1.78-1.69 (1H, m, C*H*HCH$_2$OSi), 1.46-1.36 (1H, m, CH*H*CH$_2$OSi), 1.11-0.97 (24H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.2 (2 x Ph-C_{para}), 131.8 (d, *J* 10, 4 x Ph-C_{meta}), 131.8 (d, *J* 137, 2 x Ph-C_{ipso}), 128.6 (d, *J* 13, 4 x Ph-C_{ortho}), 69.6 (d, *J* 6, CH_2OP), 61.2 (CH_2OSi), 36.4 (*C*H$_2$CH$_2$OSi), 31.2 (d, *J* 7, *C*HCH$_3$), 18.2 (SiCH*C*H$_3$),

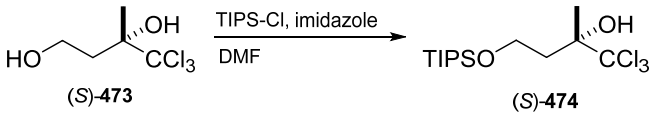
16.8 (CH*C*H_3), 12.1(Si*C*HCH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{26}H_{41}NaO_3Psi$ $[M+Na]^+$ 483.2455, found 483.2453.

(*S*)-4,4,4-Trichloro-3-methylbutane-1,3-diol 473



To a solution of (*S*)-4-methyl-4-(trichloromethyl)oxetan-2-one **171** (1.02 g, 5.02 mmol) in dry THF (25 mL) was added $LiBH_4$ (0.331 g, 15.06 mmol) at 0 °C under nitrogen, and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with water and filtered through celite with EtOAc. The solvent was removed *in vacuo* to yield product as a white solid (0.949 g, 92%). ν (cm^{-1}); 3355 (br, O-H stretch), 1127 (C-O stretch), 788 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06-3.94 (2H, m, C*H*$_2$OH), 3.50 (1H, s, OH), 2.47 (1H, ddd, *J* 14.5, 9.5, 4.5, C*H*HCH_2OH), 2.16 (1H, dd, *J* 6, 4, OH), 2.09 (1H, dt, *J* 14.5, 4, CH*H*CH_2OH), 1.68 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.1 (CCl_3), 83.4 (*C*(CH_3)), 59.7 (CH_2OH), 37.0 (*C*H_2CH_2OH), 22.5 (CH_3); m.p = 46-47 °C; $[\alpha]_D^{25}$ +9.7 (*c* 0.16, $CHCl_3$).

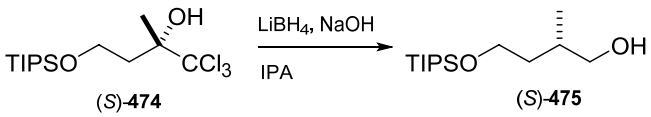
(*S*)-1,1,1-Trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol 474



To a solution of (*S*)-4,4,4-trichloro-3-methylbutane-1,3-diol **473** (1.89 g, 9.13 mmol) in DMF (18 mL) was added imidazole (0.746 g, 11.0 mmol) and triisopropylsilyl chloride (2.35 mL, 11.0 mmol) under nitrogen, and the solution was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with pH 2 buffer,

water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (40:1 petroleum ether/Et_2O) to yield product as a colourless oil (2.50 g, 76%). ν (cm^{-1}); 3445 (br, O-H stretch), 2942 (C-H stretch), 1107 (C-O stretch), 881 (Si-O stretch), 794 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (1H, s, OH), 4.14-4.04 (2H, m, CH_2OSi), 2.48 (1H, ddd, *J* 14.5, 10.5, 4.5, C*H*HCH_2OSi), 2.01 (1H, ddd, *J* 14.5, 3.5, 3, CH*H*CH_2OSi), 1.66 (3H, s, $OC(CH_3)$), 1.89-1.01 (21H, m, Si(C*H*(CH_3)$_2$)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.1 (CCl_3), 83.0 (C(OH)), 60.9 (CH_2OSi), 37.1 (*C*H_2CH_2OSi), 22.7 (OC(*C*H_3)), 18.1 (SiCH*C*H_3), 11.8 (Si*C*HCH_3); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{29}{}^{35}Cl_3NaO_2Si$ $[M+Na]^+$ 385.0895, found 385.0898; $[\alpha]_D{}^{25}$ +27.6 (*c* 0.31, $CHCl_3$).

(*S*)-2-Methyl-4-((triisopropylsilyl)oxy)butan-1-ol 475

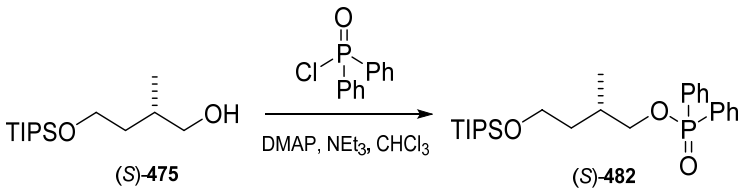


(*S*)-**474** (*S*)-**475**

To a solution of (*S*)-1,1,1-trichloro-2-methyl-4-((triisopropylsilyl)oxy)butan-2-ol **474** (1.64 g, 4.53 mmol) in dry propan-2-ol (20 mL) was added $LiBH_4$ (0.400 g, 18.1 mmol) and freshly powdered NaOH (0.544 g, 13.6 mmol) under nitrogen. The mixture was stirred at room temperature until the reaction was complete by TLC (16 h), when it was quenched with saturated NH_4Cl (aq.) (5 mL). The aqueous phase was saturated with solid NaCl and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (9:1 petroleum ether/EtOAc) to yield product as a colourless oil (0.630 g, 54%) after column chromatography (9:1 petroleum ether/EtOAc). ν (cm^{-1}); 3338 (br, O-H stretch), 2923 (C-H stretch), 1095 (C-O stretch), 881 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (1H, dt, *J* 10.5, 5, C*H*HOSi), 3.74 (1H, dt, *J* 10.5, 6, CH*H*OSi), 3.53 (1H, ddd, *J* 11, 7.5, 4.5, C*H*HOH), 3.43 (1H, ddd, *J* 11, 7, 5,

CH*H*OH), 3.08 (1H, dd, *J* 7.5, 5, OH), 1.89-1.78 (1H, m, C*H*CH_3), 1.61-1.55 (2H, m, C*H*$_2$$CH_2$OSi), 1.17-1.03 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.93 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.4 (CH_2OH), 62.2 (CH_2OSi), 37.9 (*C*H_2CH_2OSi), 34.8 (*C*HCH_3), 18.1 (SiCH*C*H$_3$), 17.6 (CH*C*H$_3$), 12.0 (Si*C*HCH$_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{32}NaO_2Si$ $[M+Na]^+$ 283.2064, found 283.2062; $[\alpha]_D^{25}$ -7.0 (*c* 0.57, $CHCl_3$). Spectroscopic data are consistent with that previously reported.[295]

(*S*)-2-Methyl-4-((triisopropylsilyl)oxy)butyl diphenylphosphinate 482

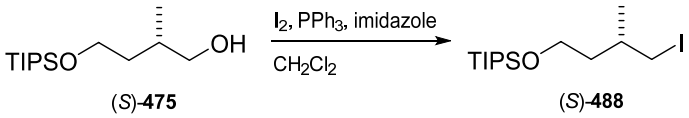


(*S*)-**475** (*S*)-**482**

To a solution of (*S*)-2-methyl-4-((triisopropylsilyl)oxy)butan-1-ol **475** (36.5 mg, 0.140 mmol) in dry $CHCl_3$ (2 mL) was added NEt_3 (58.0 µL, 1.04 mmol), DMAP (17.0 mg, 0.140 mmol) and diphenyl phosphinic chloride (40.0 µL, 0.211 mmol) under nitrogen. The mixture was stirred at room temperature until complete by TLC, quenched with saturated $NaHCO_3$ (aq.) and extracted with CH_2Cl_2. The combined organic fractions were washed with saturated $NaHCO_3$ (aq.), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether/EtOAc) to yield product as a colourless oil (53.0 mg, 82%, ≥ 98% *e.e.*) after column chromatography (7:3 petroleum ether/EtOAc). ν (cm^{-1}); 2940 (C-H stretch), 1438 (P-Ph stretch), 1229 (P=O stretch), 1099 (Si-O stretch), 690 (Si-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85-7.76 (4H, m, Ph-H), 7.54-7.48 (2H, m, Ph-H), 7.47-7.71 (4H, m, Ph-H), 3.91 (1H, dt, *J* 9.5, 5.5, C*H*HOP), 3.85 (1H, dt, *J* 9.5, 6, CH*H*OP), 3.76-3.68 (2H, m, CH_2OSi), 2.13-2.03 (1H, m, C*H*CH_3), 1.78-1.69 (1H, m, C*H*HCH_2OSi), 1.45-1.36 (1H, m, CH*H*CH_2OSi), 1.10-0.96 (24H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$) and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.2 (2 x Ar-C_{para}),

131.8 (d, *J* 10, 4 x Ar-C_{meta}), 131.8 (d, *J* 137, 2 x Ar-C_{ipso}), 128.6 (d, *J* 13, 4 x Ar-C_{ortho}), 69.6 (CH_2OP), 61.2 (CH_2OSi), 36.4 (CH_2CH_2OSi), 31.2 ($CHCH_3$), 18.2 ($SiCHCH_3$), 16.8 ($CHCH_3$), 12.1 ($SiCHCH_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{26}H_{41}NaO_3PSi$ $[M+Na]^+$ 483.2455, found 483.2459; $[\alpha]_D^{25}$ +2.1 (*c* 0.52, $CHCl_3$). Enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiracel AD-H column, 2-propanol : hexane = 2 : 98, 1 mL/min, 226 nm, (*S*) isomer 33.81 min, (*R*) isomer 38.80 min).

(*S*)-(4-Iodo-3-methylbutoxy)triisopropylsilane 488

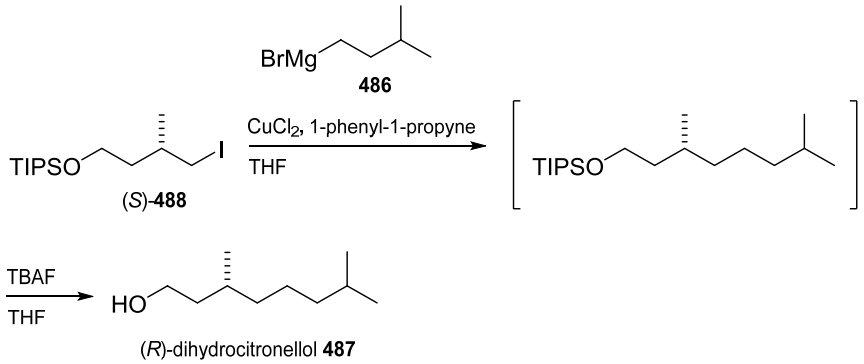


(*S*)-**475** (*S*)-**488**

To a solution of imidazole (48.0 mg, 0.703 mmol) and PPh_3 (0.175 g, 0.670 mmol) in CH_2Cl_2 (2 mL) was added I_2 (0.179 g, 0.703 mmol) at 0 °C and the mixture was stirred at this temperature for 15 minutes. (*S*)-2-Methyl-4-((triisopropylsilyl)oxy)butan-1-ol **475** (0.145 g, 0.558 mmol) in CH_2Cl_2 (1 mL) was then added dropwise and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated $Na_2S_2O_3$ (aq.), extracted with CH_2Cl_2 and the solvent was removed *in vacuo*. Purification by column chromatography (100% petroleum ether) yielded product as an orange oil (0.163 g, 81%). ν (cm^{-1}); 2918 (C-H stretch), 1102 (Si-O stretch), 881 (Si-O stretch), 657 (C-I stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77-3.68 (2H, m, CH_2OSi), 3.30 (1H, dd, *J* 9.5, 4.5, C*H*HI), 3.22 (1H, dd, *J* 9.5, 6, CH*H*I), 1.73-1.66 (1H, m, C*H*CH_3), 1.66-1.58 (1H, m, C*H*HCH_2OSi), 1.49-1.41 (1H, m, CH*H*CH_2OSi), 1.13-1.02 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.00 (3H, d, *J* 6.5, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 61.1 (CH_2OSi), 39.5 (CH_2CH_2OSi), 31.5 ($CHCH_3$), 20.9 ($CHCH_3$), 18.5 (CH_2I), 18.2 ($SiCHCH_3$), 12.1 ($SiCHCH_3$); HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{31}INaOSi$

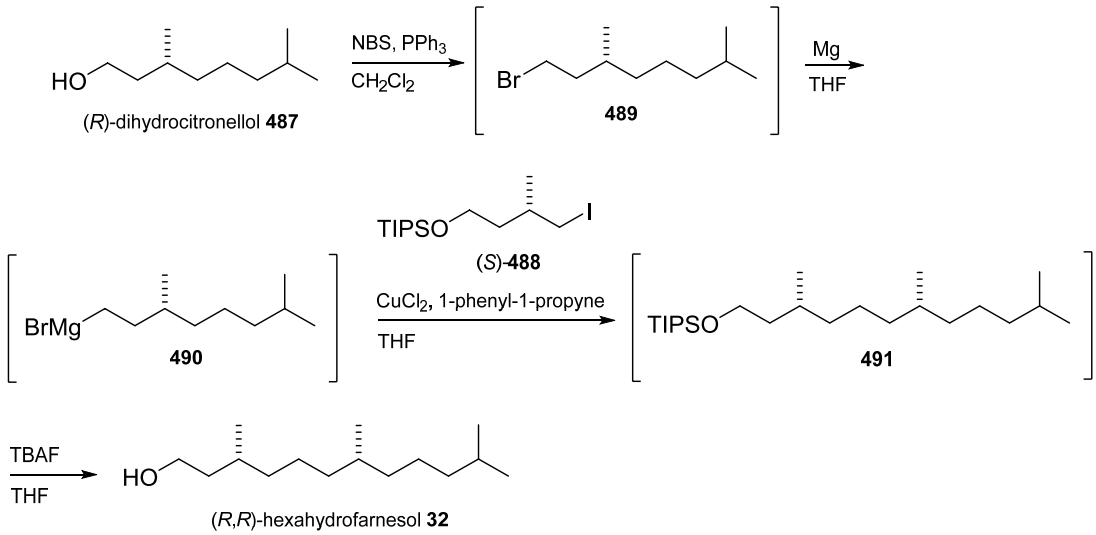
$[M+Na]^+$ 393.1081, found 393.1067; $[\alpha]_D^{25}$ +6.7 (*c* 0.39, $CHCl_3$). This compound was reported previously but without spectroscopic data.[466]

(*R*)-Dihydrocitronellol 487



To a mixture of (*S*)-(4-iodo-3-methylbutoxy)triisopropylsilane **488** (0.486 g, 1.35 mmol), $CuCl_2$ (5.50 mg, 0.0405 mmol) and 1-phenyl-1-propyne (26.0 µL, 0.205 mmol) in THF (4.5 mL) was added *i*-pentylmagnesium bromide **486** (1.37 mL, 2M in THF, 2.74 mmol) at 0 °C. The reaction was stirred for two hours at this temperature then quenched with saturated NH_4Cl (aq.). The mixture was extracted with Et_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. To a solution of this crude product in THF (1.8 mL) was added TBAF (2.00 mL, 1M in THF, 2.00 mmol) at 0 °C under nitrogen, then stirred at room temperature for three hours. The reaction was quenched with ice water, extracted with Et_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (9:1 petroleum ether/EtOAc) to yield product as a colourless oil (0.144 g, 68%). ν (cm^{-1}); 3333 (br, O-H stretch), 2924 (C-H stretch), 1052 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.74-3.61 (2H, m, C*H*$_2$OH), 1.65-1.06 (10H, m, $CH_2CH(CH_2)_3CH$), 0.94-0.81 (9H, overlapping d's, C*H*$_3$CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 61.4 (CH_2OH), 40.1, 39.4, 37.5 (CH_2), 29.6, 28.1 (CH), 24.8 (CH_2), 22.8, 22.7, 19.8 (CH_3); GC/MS (CI, NH_3): 176.1 $[M+NH_4]^+$. The spectroscopic data are consistent with that previously reported.[450, 467]

(*R*,*R*)-Hexahydrofarnesol 32



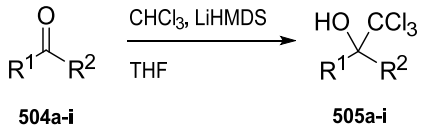
To a solution of (*R*)-dihydrocitronellol **487** (0.128 g, 0.810 mmol) in CH_2Cl_2 (8 mL) was added PPh_3 (0.255 g, 0.972 mmol), and the mixture was cooled to 0 °C. *N*-bromosuccinimide (0.160 g, 0.899 mmol) was then added in portions over a period of 30 minutes, at 0 °C. The reaction was stirred for a further 20 minutes at room temperature, then the solvent was removed under a flow of nitrogen. The residue was passed through a short plug of silica eluting with *n*-pentane, to yield (*R*)-1-bromo-3,7-dimethyloctane **489** (0.160 g, 89%) as a colourless oil. This compound was used immediately in the next step. A solution of bromide **489** (0.136 g, 0.615 mmol) in dry THF (0.5 mL) was added to magnesium turnings (22.0 mg, 0.923 mmol) in THF (0.5 mL), and the mixture was stirred at room temperature for 30 minutes then at reflux temperature for two hours. A solution of this Grignard reagent **490** was then added to a solution of iodide (*S*)-**488** (0.111 g, 0.308 mmol), $CuCl_2$ (4.00 mg, 0.0308 mmol) and 1-phenyl-1-propyne (5.70 µL, 0.0462 mmol) in dry THF (1.5 mL), at 0 °C. The resultant solution was stirred at 0 °C for 30 minutes then at room temperature for a further two hours. The reaction was quenched with saturated NH_4Cl (aq.), extracted with Et_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The protected alcohol **491** was used directly in the next step as a crude material. To a solution of **491**

in THF (0.7 mL) was added TBAF (1M, 0.616 mL, 0.616 mmol) at 0 °C, under nitrogen. The solution was warmed to room temperature and stirred until the reaction was complete by TLC (three hours). The reaction was quenched with cold water, extracted with Et_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (100% petroleum ether to 9:1 petroleum ether/EtOac to 85:15) to yield (*R*,*R*)-hexahydrofarnesol **32** as a colourless oil (9 mg, 13% from iodide (*S*)-**488**). The title compound was inseparable from impurities. Only ^{1}H NMR and GC/MS (EI) data were obtained. ^{1}H NMR (500 MHz, $CDCl_3$) 3.76-3.59 (2H, m, C*H*$_2$OH), 1.67-0.99 (18H, m, CH_2 and CH), 0.94-0.79 (12H, m, C*H*$_3$CH); GC/MS (EI): 210.0 $[M\text{-}H_2O]^+$. The ^{1}H NMR data are consistent with that previously reported.[450]

Preparation of lithium hexamethyldisilazide (LiHMDS)

A solution of 1M LiHMDS can be prepared by the following procedure. A solution of hexamethyldisilazane (HMDS) (0.23 mL, 1.1 mmol) in dry THF (0.37 mL) was placed under nitrogen and cooled to -78 °C. *n*-BuLi (2.5M in THF, 1.00 mmol, 0.40 mL) was then added dropwise, and the solution was stirred at -78 °C for 30 minutes. After this time the LiHMDS was used in the reactions shown below.

Synthesis of Trichloromethyl Carbinols: General Procedure 1

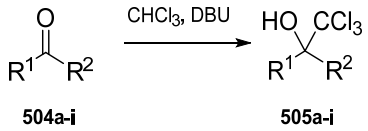


504a-i **505a-i**

To a solution of ketone (1.00 equiv.) and dry $CHCl_3$ (2.50 equiv.) in dry THF (4 mL/mmol ketone), was added freshly prepared LiHMDS (1.00 M in THF, 2.20 equiv.) dropwise at -78 °C, under nitrogen. The mixture was stirred at -78 °C for one hour then quenched with saturated NH_4Cl (aq.). The product was extracted with Et_2O, the

combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc).

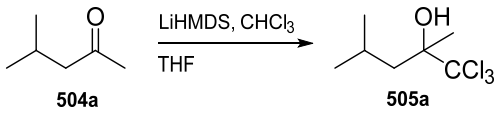
Synthesis of Trichloromethyl Carbinols: General Procedure 2



504a-i **505a-i**

To a solution of ketone (1.00 equiv.) in dry $CHCl_3$ (2.00 equiv.) was added DBU (1.00 equiv.) under nitrogen. The mixture was stirred at room temperature for 24 hours, diluted with CH_2Cl_2 and washed with 1M HCl (aq.), water and brine. The solvent was removed *in vacuo* and the residue was purified by column chromatography (petroleum ether/EtOAc).

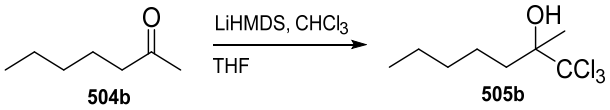
1,1,1-Trichloro-2,4-dimethylpentan-2-ol 505a



504a **505a**

The compound was prepared according to General Procedure 1 (using 0.120 mL, 1.00 mmol 4-methylpentan-2-one **504a**) to yield product as a yellow oil (0.138 g, 63%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3451 (br, O-H stretch), 1131 (C-O stretch), 774 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (1H, s, OH), 1.98-1.88 (2H, m, C*H*HC(OH) and C*H*$(CH_3)_2$), 1.83-1.75 (1H, m, CH*H*C(OH)), 1.60 (3H, s, OC(CH_3)), 1.06 (3H, d, *J* 6.5, C*H*$_3$CH), 1.01 (3H, d, *J* 6.5, C*H*$_3$CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.6 (CCl_3), 83.6 (C(OH)), 43.8 (CH_2), 25.2, 25.1 (*C*H_3CH), 23.9 (CH_3C*H*), 21.5 (OC(*C*H_3)); GC/MS (EI): 130.0, 132.0 [M-Cl_2H_2O]$^+$. This compound was previously reported without spectroscopic data.[468]

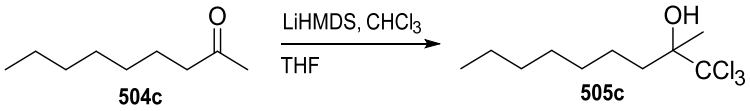
1,1,1-Trichloro-2-methylheptan-2-ol 505b



504b 505b

The compound was prepared according to General Procedure 1 (using 0.290 mL, 2.00 mmol 2-heptanone **504b**) to yield product as a colourless oil (0.429 g, 92%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3456 (br, O-H stretch), 2925 (C-H stretch), 1139 (C-O stretch), 787 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (1H, s, OH), 2.00-1.90 (2H, m, C*H*$_2$C(OH)) 1.62-1.52 (1H, m, C*H*HCH$_2$C(OH)), 1.56 (3H, s, OC(CH$_3$)), 1.50-1.40 (1H, m, CH*H*CH$_2$C(OH)), 1.39-1.29 (4H, m, CH$_2$), 0.92 (3H, t, *J* 7, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.4 (CCl_3), 83.2 (C(OH)), 35.8 (*C*H$_2$C(OH)), 32.3 (CH$_2$), 24.2 (*C*H$_2$CH$_2$C(OH)), 22.8 (CH$_2$), 21.3 (OC(*C*H$_3$)), 14.2 (*C*H$_3$CH$_2$); GC/MS (EI): 143.2 $[M\text{-}Cl_2H_2O]^+$. This compound was previously reported without ^{1}H and ^{13}C NMR data.[469, 470]

1,1,1-Trichloro-2-methylnonan-2-ol 505c

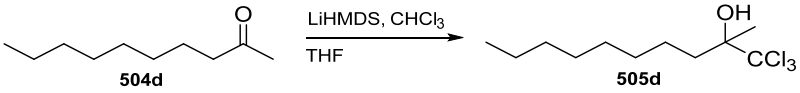


504c 505c

The compound was prepared according to General Procedure 1 (using 0.35 mL, 2.00 mmol 2-nonanone **504c**) to yield product as a colourless oil (0.376 g, 72%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3452 (br, O-H stretch), 2955 (C-H stretch), 1139 (C-O stretch), 788 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.24 (1H, s, OH), 2.00-1.89 (2H, m, C*H*$_2$C(OH)), 1.62-1.51 (1H, m, C*H*HCH$_2$C(OH)), 1.57 (3H, s, OC(CH$_3$)), 1.49-1.39 (1H, m, CH*H*CH$_2$C(OH)), 1.38-1.22 (8H, m, CH$_2$), 0.94-0.82 (3H, m, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.4 (CCl_3), 83.2 (C(OH)), 35.8 (*C*H$_2$C(OH)), 31.9, 30.1, 29.4 (CH$_2$), 24.5

(*C*H_2CH_2C(OH)), 22.8 (CH_2), 21.3 (OC(*C*H_3)), 14.2 (*C*H_3CH_2); GC/MS (EI): 171.2 [M-Cl_2H_2O]$^+$.

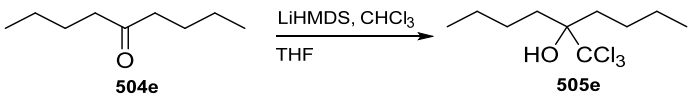
1,1,1-Trichloro-2-methyldecan-2-ol 505d



504d **505d**

The compound was prepared according to General Procedure 1 (using 0.380 mL, 2.00 mmol 2-decanone **504d**) to yield product as a colourless oil (0.380 g, 69%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3452 (br, O-H stretch), 2924 (C-H stretch), 1105 (C-O stretch), 785 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.22 (1H, s, OH), 2.00-1.89 (2H, m, C*H*$_2$C(OH)), 1.61-1.51 (1H, m, C*H*HCH_2C(OH)), 1.56 (3H, s, OC(CH_3)), 1.49-1.39 (1H, m, CH*H*CH_2C(OH)), 1.39-1.22 (10H, m, CH_2), 0.92-0.85 (3H, m, C*H*$_3CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.4 (CCl_3), 83.2 (C(OH)), 35.9 (*C*H_2C(OH)), 32.0, 30.2, 29.7, 29.4 (CH_2), 24.5 (*C*H_2CH_2C(OH)), 22.8 (CH_2), 21.3 (OC(*C*H_3)), 14.3 (*C*H_3CH_2); GC/MS (EI): 185.2 [M-Cl_2H_2O]$^+$.

5-(Trichloromethyl)nonan-5-ol 505e

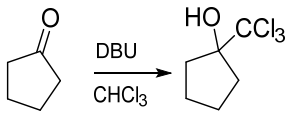


504e **505e**

The compound was prepared according to General Procedure 1 (using 0.340 mL, 2.00 mmol 5-nonanone **504e**) to yield product as a colourless oil (0.319 g, 61%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3473 (br, O-H stretch), 2958 (C-H stretch), 1131 (C-O stretch), 776 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (1H, s, OH), 2.05-1.87 (4H, m, C*H*$_2$C(OH)), 1.52-1.42 (4H, m, C*H*$_2CH_2$C(OH)), 1.41-1.31 (4H, m, CH_3C*H*$_2$), 0.95 (6H, t, *J* 7.5, C*H*$_3CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.7 (CCl_3), 83.9 (C(OH)), 35.2 (*C*H_2C(OH)), 27.1

($CH_2CH_2C(OH)$), 23.6 (CH_3CH_2), 14.2 (CH_3CH_2); GC/MS (EI): 225 $[M-^{37}Cl]^+$, 189.2 $[M-Cl_2]^+$, 171.2 $[M-Cl_2H_2O]^+$. This compound was previously reported without ^1H or ^{13}C NMR data.[470]

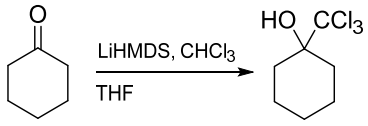
1-(Trichloromethyl)cyclopentan-1-ol 505f



504f **505f**

The compound was prepared according to General Procedure 2 (using 0.890 mL, 10.0 mmol cyclopentanone **504f**) to yield product as a white solid (0.872 g, 43%) after column chromatography (9:1 petroleum ether/EtOAc). ν (cm^{-1}); 3399 (br, O-H stretch), 2964 (C-H stretch), 772 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.40 (1H, s, OH), 2.39-2.30 (2H, m, C*H*HC(OH)), 2.00-1.90 (2H, m, C*H*HCH_2C(OH)), 1.88-1.75 (4H, m, CH*H*C(OH) and CH*H*CH_2C(OH)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 107.5 (CCl_3), 92.6 (C(OH)), 37.4 (CH_2C(OH)), 25.6 (CH_2CH_2C(OH)); GC/MS (EI): 97 $[M-Cl_3]^+$; m.p = 35-36 °C. Spectroscopic data are consistent with that previously reported.[471]

1-(Trichloromethyl)cyclohexan-1-ol 505g

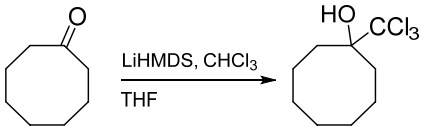


504g **505g**

The compound was prepared according to General Procedure 1 (using 0.210 mL, 2.00 mmol cyclohexanone **504g**) to yield product as a white solid (0.241 g, 55%) after column chromatography (92:8 petroleum ether/EtOAc). ν (cm^{-1}); 3451 (br, O-H stretch), 2936 (C-H stretch), 1159 (C-O stretch), 773 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13-2.01 (3H, m, C*H*HC(OH) and OH), 1.90 (2H, td, *J* 13.5, 4,

CH*H*C(OH)), 1.78-1.69 (3H, m, C*H*HCH$_2$C(OH) and C*H*HCH$_2$CH$_2$), 1.63 (2H, qt, *J* 13, 3.5, CH*H*CH$_2$C(OH)), 1.21-1.10 (1H, m, CH*H*CH$_2$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 110.5 (CCl_3), 81.9 (C(OH)), 31.4 (*C*H$_2$C(OH)), 25.1 (*C*H$_2$CH$_2$CH$_2$), 22.0 (*C*H$_2$CH$_2$C(OH)); GC/MS (EI): 181.1 [M-^{35}Cl]$^+$, 163.2 [M-^{35}ClH$_2$O]$^+$; m.p = 60-61 °C. Spectroscopic data are consistent with that previously reported.[471]

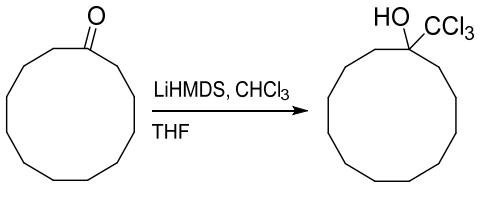
1-(Trichloromethyl)cyclooctan-1-ol 505h



504h **505h**

The compound was prepared according to General Procedure 1 (using 0.252 g, 2.00 mmol cyclooctanone **504h**) to yield product as a colourless oil (0.260 g, 53%) after column chromatography (9:1 petroleum ether/Et$_2$O). ν (cm^{-1}); 3453 (br, O-H stretch), 2920 (C-H stretch), 1138 (C-O stretch), 757 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29-2.08 (4H, m, C*H*$_2$C(OH)), 1.85-1.73 (4H, m, C*H*$_2$CH$_2$C(OH)), 1.72-1.59 (3H, m, CH$_2$), 1.58-1.44 (3H, m, CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 111.4 (CCl_3), 84.2 (C(OH)), 31.9 (*C*H$_2$C(OH)), 27.8 (CH$_2$), 24.6 (CH$_2$), 22.4 (*C*H$_2$CH$_2$C(OH)); GC/MS (EI): 191.1 [M-^{37}ClH$_2$O]$^+$, 155.2 [M-^{35}Cl$_2$H$_2$O]$^+$.

1-(Trichloromethyl)cyclododecan-1-ol 505i

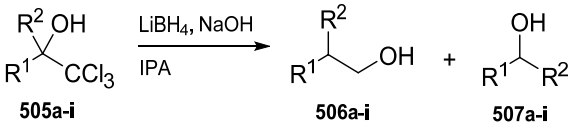


504i **505i**

The compound was prepared according to General Procedure 1 (using 0.354 g, 2.00 mmol cyclododecanone **504i**) to yield product as a colourless oil (0.400 g, 67%) after column chromatography (95:5 petroleum ether/EtOAc). ν (cm^{-1}); 3453 (br, O-H

stretch), 2927 (C-H stretch), 1067 (C-O stretch), 785 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (1H, s, OH), 2.06-1.90 (4H, m, C*H*$_2$C(OH)), 1.64-1.46 (4H, m, C*H*$_2$CH$_2$C(OH)), 1.45-1.30 (14H, m, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.9 (CCl_3), 84.8 (C(OH)), 31.6 (*C*H$_2$C(OH)), 26.8 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 22.3 (CH_2), 21.2 (*C*H$_2$CH$_2$C(OH)); GC/MS (EI): 229.3 [M-$^{35}Cl_2$]$^+$.

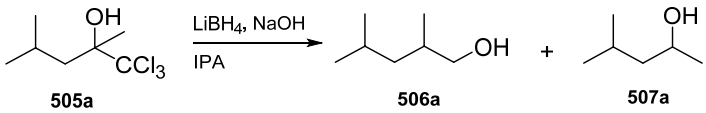
Jocic Reaction: General Procedure 3



505a-i **506a-i** **507a-i**

To a solution of trichloromethylcarbinol (1.00 equiv.) in dry propan-2-ol (4 mL/mmol substrate) was added $LiBH_4$ (4.00 equiv.) and NaOH (3.00 equiv.) under nitrogen, and stirred for 16 hours at 40 °C. The reaction was quenched with saturated NH_4Cl (aq.) and brine was added. The product was extracted with EtOAc (5 x 10 mL), the combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc).

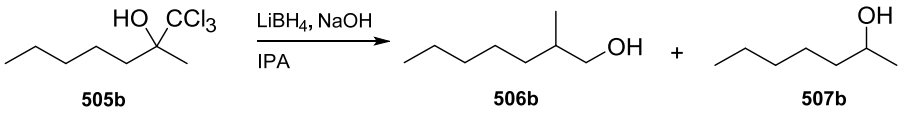
2,4-Dimethylpentan-1-ol 506a



505a **506a** **507a**

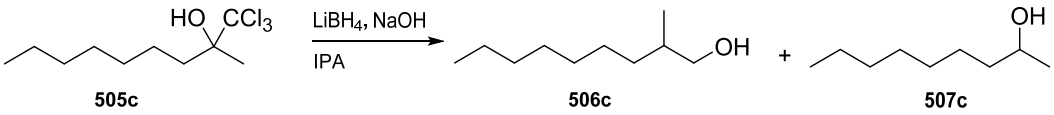
The reaction was carried out according to General Procedure 3 (using 0.268 g, 1.22 mmol 1,1,1-trichloro-2,4-dimethylpentan-2-ol **505a**) to yield crude product as a colourless oil (20.0 mg, 14%). Integration of the peaks at 3.95-3.80 ppm[472] (1H, m, **507**-C*H*OH) and 3.45-3.33 ppm[473] (1H, m, **506**-C*H*HOH) in the ^{1}H NMR spectrum provided a ratio of **506**:**507** = 70:30. No further data were obtained for this crude mixture.

2-Methylheptan-1-ol 506b



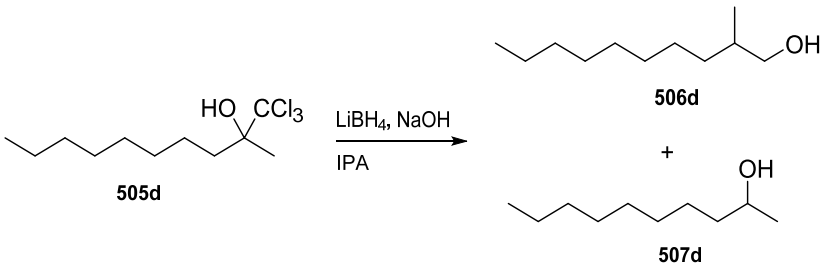
The reaction was carried out according to General Procedure 3 (using 0.385 g, 1.65 mmol 1,1,1-trichloro-2-methylheptan-2-ol **505b**) to yield crude product as a colourless oil (0.147 g, 69%). Integration of the peaks at 3.88-3.73 ppm[474] (1H, m, **507**-C*H*OH) and 3.47-3.36 ppm[475] (1H, m, **506**-C*H*HOH) in the ^{1}H NMR spectrum provided a ratio of **506**:**507** = 82:18. No further data were obtained for this crude mixture.

2-Methylnonan-1-ol 506c



The reaction was carried out according to General Procedure 3 (using 0.270 g, 1.03 mmol 1,1,1-trichloro-2-methylnonan-2-ol **505c**) to yield crude product as a colourless oil (97 mg, 65%). Integration of the peaks at 3.86-3.72 ppm[476] (1H, m, **507**-C*H*OH) and 3.46-3.36 ppm (1H, m, **506**-C*H*HOH) in the ^{1}H NMR spectrum provided a ratio of **506**:**507** = 77:23. No further data were obtained for this crude mixture.

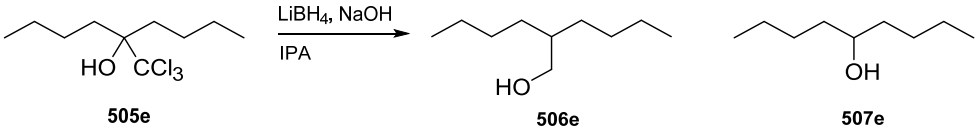
2-Methyldecan-1-ol 506d



The reaction was carried out according to General Procedure 4 (using 0.140 g, 0.51 mmol 1,1,1-trichloro-2-methyldecan-2-ol **505d**) to yield crude product as a colourless oil (73.0 mg, 90%). Integration of the peaks at 3.86-3.75 ppm[477] (1H, m, **507**-C*H*OH)

and 3.46-3.36 ppm[478] (1H, m, **506**-C*H*HOH) in the ^{1}H NMR spectrum provided a ratio of **506**:**507** = 82:18. No further data were obtained for this crude mixture.

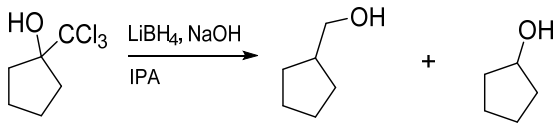
2-Butylhexan-1-ol 506e



505e **506e** **507e**

The reaction was carried out according to General Procedure 3 (using 0.266 g, 1.02 mmol 5-(trichloromethyl)nonan-5-ol **505e**) to yield crude product as a colourless oil (0.143 g, 90%). Integration of the peaks at 3.62-3.55 ppm[479] (1H, m, **507**-C*H*OH) and 3.53 ppm[480] (2H, d, *J* 5.5, **506**-C*H*$_2$OH) provided an approximate ratio of **506**:**507** = 45:55 as the peaks were slightly overlapping. No further data were obtained for this crude mixture.

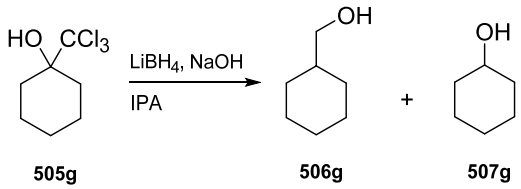
Cyclopentylmethanol 506f



505f **506f** **507f**

The reaction was carried out according to General Procedure 3 (using 98.0 mg, 0.484 mmol 1-(trichloromethyl)cyclopentan-1-ol **505f**) to yield crude product as a colourless oil (32.0 mg, 70%). Integration of the peaks at 4.37-4.30 ppm[472] (1H, m, **507**-C*H*OH) and 3.51 ppm[481] (2H, d, *J* 7, **506**-C*H*$_2$OH) provided a ratio of **506**:**507** = 95:5. No further data were obtained for this crude mixture.

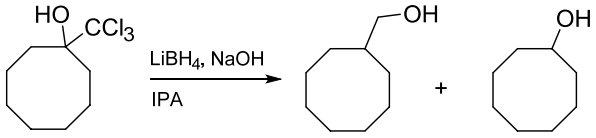
Cyclohexylmethanol 506g



505g **506g** **507g**

The reaction was carried out according to General Procedure 3 (using 0.190 g, 0.880 mmol 1-(trichloromethyl)cyclohexan-1-ol **505g**) to yield crude product as a colourless oil (85.0 mg, 76%). Integration of the relevant peaks at 3.67-3.54 ppm[482] (1H, m, **507**-C*H*OH) and 3.44 ppm[483] (2H, d, *J* 6, **506**-CH_2OH) provided a ratio of **506**:**507** = 73:17. No further data were obtained for this crude mixture.

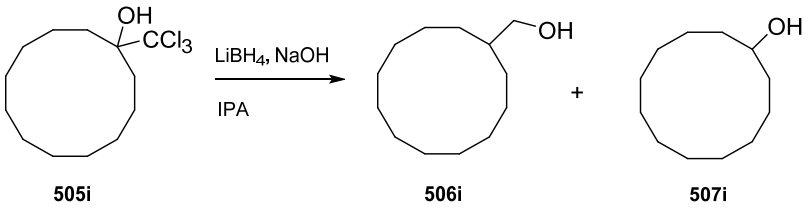
Cyclooctylmethanol 506h



505h **506h** **507h**

The reaction was carried out according to General Procedure 3 (using 0.240 g, 0.980 mmol 1-(trichloromethyl)cyclooctan-1-ol **505h**) to yield crude product as a colourless oil (0.115 g, 82%). Integration of the relevant peaks at 3.85 ppm[484] (1H, tt, *J* 8.5, 4, **507**-C*H*OH) and 3.44-3.34[478] (2H, m, **506**-CH_2OH) provided a ratio of **506**:**507** = 21:79. No further data were obtained for this crude mixture.

Cyclododecylmethanol 506i



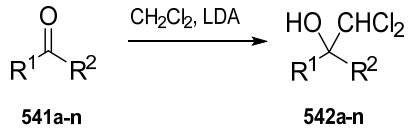
505i **506i** **507i**

The reaction was carried out according to General Procedure 3 (using 0.342 g, 1.14 mmol 1-(trichloromethyl)cyclododecan-1-ol **505i**) to yield crude product as a colourless oil (0.214 g, 95%). Integration of the relevant peaks at 3.90-3.79 ppm[485] (1H, m, **507**-C*H*OH) and 3.49 ppm[486] (2H, d, *J* 6, **506**-C*H*$_2$OH) provided a ratio of **506**:**507** = 66:34. The primary alcohol **506i** could be separated cleanly (0.110 g, 49%) by column chromatography (8:2 petroleum ether/EtOAc). ν (cm^{-1}); 3329 (br, O-H stretch), 2926 (C-H stretch), 1039 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.49 (2H, d, *J* 6.5, C*H*$_2$OH), 1.69-1.62 (1H, m, C*H*CH$_2$OH), 1.47-1.22 (22H, m, CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 67.2 (CH_2OH), 36.9 (*C*HCH$_2$OH), 26.4, 24.5, 23.8, 23.6, 23.7, 22.2 (CH_2); GC/MS (EI): 180.6 [M-H$_2$O]$^+$. Spectroscopic data are consistent with that previously reported.[486]

General preparation of lithium diisopropylamide (LDA)

A 1M solution of LDA could be prepared using the following procedure. A solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF (0.44 mL) was placed under nitrogen and cooled to -78 °C. *n*-BuLi (0.40 mL, 2.5M in THF, 1.00 mmol) was then added and the solution was stirred at -78 °C for 30 minutes. After this time the LDA was used in the reactions shown below.

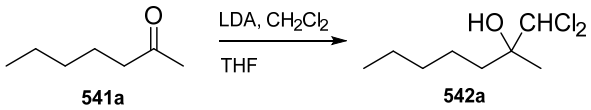
Dichloromethyllithium Addition: General Procedure 4



541a-n **542a-n**

To a solution of ketone (1.0 equiv.) in dry CH_2Cl_2 (2 mL/mmol ketone) was added freshly prepared LDA (2.0 equiv., 1M in THF) at -78 °C, under nitrogen. The reaction was stirred for 30 minutes at this temperature unless specified otherwise, then quenched with saturated NH_4Cl (aq.) (3 mL). The product was extracted with Et_2O and the combined organic fractions were washed successively with pH 2 buffer and water, then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography where necessary.

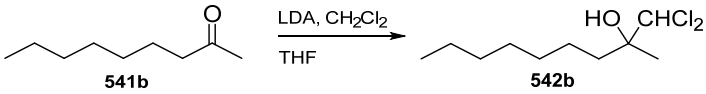
1,1-Dichloro-2-methylheptan-2-ol 542a



541a **542a**

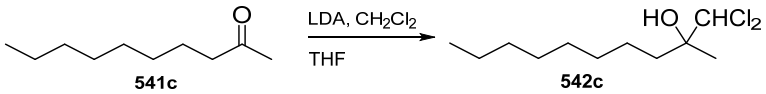
The compound was prepared according to General Procedure 4 (using 0.140 mL, 1.00 mmol 2-heptanone **541a**) to yield product as a yellow oil (0.176 g, 88%). ν (cm^{-1}); 3437 (br, O-H stretch), 2955 (C-H stretch), 1155 (C-O stretch), 772 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.68 (1H, s, $CHCl_2$), 2.04 (1H, s, OH), 1.77-1.63 (2H, m, C*H*$_2$C(OH)), 1.45-1.38 (2H, m, C*H*$_2$CH$_2$C(OH)), 1.38 (3H, s, OC(CH_3)), 1.37-1.24 (4H, m, CH_2), 0.90 (3H, t, *J* 7, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.0 ($CHCl_2$), 76.6 (C(OH)), 37.5 (*C*H$_2$C(OH)), 32.3 (CH_3*C*H$_2$), 23.0, 22.7 (CH_2), 22.1 (OC(*C*H$_3$)), 14.1 (*C*H$_3$CH$_2$); GC/MS (EI): 163.2, 165.2 $[M\text{-}Cl]^+$, 145.1, 147.1 $[M\text{-}ClH_2O]^+$, 127.1 $[M\text{-}Cl_2]^+$, 109.2 $[M\text{-}Cl_2H_2O]^+$.

1,1-Dichloro-2-methylnonan-2-ol 542b



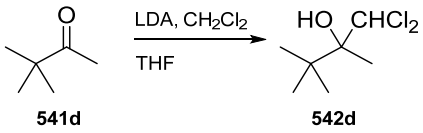
The compound was prepared according to General Procedure 4 (using 0.170 mL, 1.00 mmol 2-nonanone **541b**) to yield product as a colourless oil (0.206 g, 91%). ν (cm^{-1}); 3400 (br, O-H stretch), 2925 (C-H stretch), 1145 (C-O stretch), 772 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.68 (1H, s, $CHCl_2$), 2.05 (1H, s, OH), 1.77-1.63 (2H, m, C*H*$_2$C(OH)), 1.44-1.37 (2H, m, C*H*$_2$CH$_2$C(OH)), 1.37 (3H, s, OC(CH_3)), 1.35-1.23 (8H, m, CH_2), 0.88 (3H, t, *J* 7, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.0 ($CHCl_2$), 76.5 (C(OH)), 37.5 (*C*H$_2$C(OH)), 31.9 (CH$_3$*C*H$_2$), 30.1, 29.3, 23.3, 22.8 (CH_2), 22.1 (OC(*C*H$_3$)), 14.2 (*C*H$_3$CH$_2$); GC/MS (EI): 191.1, 193.1 $[M\text{-}Cl]^+$, 137.1 $[M\text{-}Cl_2H_2O]^+$.

1,1-Dichloro-2-methyldecan-2-ol 542c



The compound was prepared according to General Procedure 4 (using 0.190 mL, 1.00 mmol 2-decanone **541c**) to yield product as a colourless oil (0.226 g, 94%). ν (cm^{-1}); 3437 (br, O-H stretch), 2924 (C-H stretch), 1143 (C-O stretch), 773 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.68 (1H, s, $CHCl_2$), 2.04 (1H, s, OH), 1.77-1.63 (2H, m, C*H*$_2$C(OH)), 1.44-1.38 (2H, m, C*H*$_2$CH$_2$C(OH)), 1.38 (3H, s, OC(CH_3)), 1.35-1.22 (12H, m, CH_2), 0.88 (3H, t, *J* 7, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.0 ($CHCl_2$), 76.6 (C(OH)), 37.5 (*C*H$_2$C(OH)), 32.0 (CH$_3$*C*H$_2$), 30.1, 29.6, 29.4, 23.3, 22.8 (CH_2), 22.1 (OC(*C*H$_3$)), 14.3 (*C*H$_3$CH$_2$); GC/MS (EI): 205.1, 207.1 $[M\text{-}Cl]^+$, 169.1 $[M\text{-}Cl_2]^+$, 151 $[M\text{-}Cl_2H_2O]^+$.

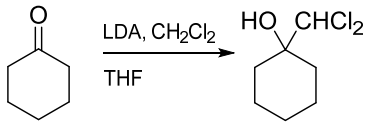
1,1-Dichloro-2,3,3-trimethylbutan-2-ol 542d



541d **542d**

The compound was prepared according to General Procedure 4 (using 0.120 mL, 1.00 mmol 3,3-dimethylbutan-2-one **541d**) to yield product as a colourless oil (60.7 mg, 33%) after column chromatography (100% petroleum ether to 95:5 petroleum ether/Et_2O). ν (cm^{-1}); 3585 (br, O-H stretch), 2959 (C-H stretch), 1110 (C-O stretch), 787 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.97 (1H, s, $CHCl_2$), 2.11-2.06 (1H, m, OH), 1.42 (3H, s, $OC(CH_3)$), 1.10 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 79.8 ($CHCl_2$), 79.3 (C(OH)), 38.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 17.3 ($OC(CH_3)$); GC/MS (EI): 149.2, 150.9 $[M\text{-}Cl]^+$, 131.0, 133.0 $[M\text{-}ClH_2O]^+$, 113.1 $[M\text{-}Cl_2]^+$, 95.2 $[M\text{-}Cl_2H_2O]^+$. Spectroscopic data are consistent with that previously reported.[487]

1-(Dichloromethyl)cyclohexan-1-ol 542e

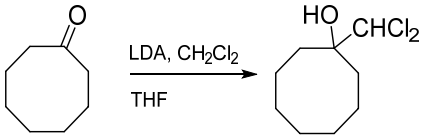


541e **542e**

The compound was prepared according to General Procedure 4 (using 0.100 mL, 1.00 mmol cyclohexanone **541e**) to yield product as a colourless oil (0.113 g, 62%) after column chromatography (9:1 petroleum ether/Et_2O). ν (cm^{-1}); 3428 (br, O-H stretch), 2934 (C-H stretch), 1150 (C-O stretch), 751 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.62 (1H, s, $CHCl_2$), 1.89 (1H, s, OH), 1.82-1.73 (2H, m, C*H*HC(OH)), 1.71-1.58 (7H, m, CH*H*C(OH) and $CH_2CH_2C(OH)$ and C*H*HCH_2CH_2), 1.24-1.14 (1H, m, CH*H*CH_2CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.9 ($CHCl_2$), 75.2 (C(OH)), 32.7 ($CH_2C(OH)$), 25.5 ($CH_2CH_2CH_2$), 21.6 ($CH_2CH_2C(OH)$); GC/MS (EI): 147.1, 149.1

$[M\text{-}Cl]^+$, 129.1, 131.1 $[M\text{-}^{35}ClH_2O]^+$, 111.2 $[M\text{-}Cl_2]^+$, 93.3 $[M\text{-}Cl_2H_2O]^+$. Spectroscopic data are consistent with that previously reported.[454, 471]

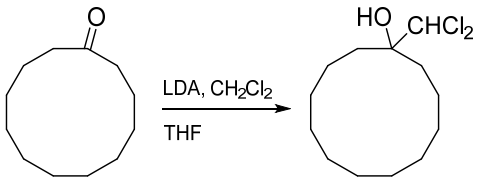
1-(Dichloromethyl)cyclooctan-1-ol 542f



541f **542f**

The compound was prepared according to General Procedure 4 (using 0.126 g, 1.00 mmol cyclooctanone **541f**) to yield product as a colourless oil (0.118 g, 56%) after column chromatography (85:15 petroleum ether/Et_2O). ν (cm^{-1}); 3440 (br, O-H stretch), 2919 (C-H stretch), 1135 (C-O stretch), 751 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, s, $CHCl_2$), 2.01-1.93 (2H, m, C*H*HC(OH)), 1.88-1.81 (2H, m, CH*H*C(OH)), 1.75-1.59 (7H, m, CH_2), 1.48-1.36 (3H, m, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.1 ($CHCl_2$), 77.8 (C(OH)), 33.1 (*C*H_2C(OH)), 28.1, 24.8, 22.0 (CH_2); GC/MS (EI): 175.1, 177.1 $[M\text{-}Cl]^+$, 157.1, 159.1 $[M\text{-}ClH_2O]^+$, 139.1 $[M\text{-}Cl_2]^+$, 121.2 $[M\text{-}Cl_2H_2O]^+$. This compound was previously reported without spectroscopic data.[488]

1-(Dichloromethyl)cyclododecan-1-ol 542g

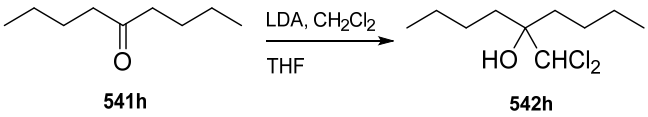


541g **542g**

The compound was prepared according to General Procedure 4 (using 0.182 g, 1.00 mmol cyclododecanone **541g**) to yield product as a colourless oil (0.190 g, 71%) after column chromatography (9:1 petroleum ether/Et_2O). ν (cm^{-1}); 3375 (br, O-H stretch), 2927 (C-H stretch), 1081 (C-O stretch), 744 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, s, $CHCl_2$), 1.95 (1H, s, OH), 1.89-1.80 (2H, m, C*H*HC(OH)), 1.63-

1.56 (2H, m, CH*H*C(OH)), 1.52-1.22 (18H, m, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.3 ($CHCl_2$), 78.7 (C(OH)), 32.0 (*C*H_2C(OH)), 26.4, 26.1, 22.6, 22.1, 20.0 (CH_2); GC/MS (EI): 231.2, 233.2 $[M\text{-}Cl]^+$, 211.3 $[M\text{-}Cl_2H_2O]^+$, 195.3 $[M\text{-}Cl_2]^+$; m.p = 58-59 °C.

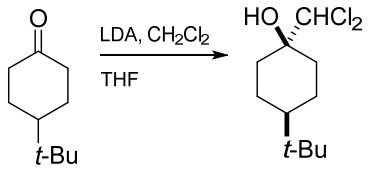
5-(Dichloromethyl)nonan-5-ol 542h



541h **542h**

The compound was prepared according to General Procedure 4 (using 0.170 mL, 1.00 mmol 5-nonanone **541h**) to yield product as a colourless oil (0.177 g, 78%) after column chromatography (9:1 petroleum ether/Et_2O). ν (cm^{-1}); 3468 (br, O-H stretch), 2956 (C-H stretch), 1145 (C-O stretch), 771 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.79 (1H, s, $CHCl_2$), 1.90 (1H, s, OH), 1.78-1.66 (4H, m, C*H*$_2$C(OH)), 1.39-1.28 (8H, m, C*H*$_2$C*H*$_2$$CH_3$), 0.93 (6H, t, *J* 7, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.5 ($CHCl_2$), 77.8 (C(OH)), 34.8 (*C*H_2C(OH)), 25.3, 23.3 (CH_2), 14.1 (CH_3); GC/MS (EI): 191.2, 193.1 $[M\text{-}Cl]^+$, 155.2 $[M\text{-}Cl_2]^+$, 137.4 $[M\text{-}Cl_2H_2O]^+$.

***cis*-4-(*tert*-Butyl)-1-(dichloromethyl)cyclohexan-1-ol 542i**

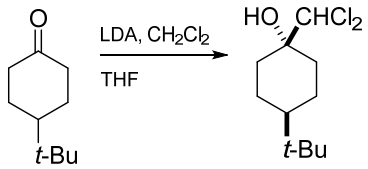


541i ***cis*-542i**

The compound was prepared according to General Procedure 4 (using 0.154 g, 1.00 mmol 4-*tert*-butylcyclohexanone **541i**) to yield product as a white solid (0.106 g, 44%) after column chromatography to separate the 1.6:1 mixture of diastereoisomers (8:2 petroleum ether/Et_2O). ν (cm^{-1}); 3501 (br, O-H stretch), 2957 (C-H stretch), 1017 (C-O stretch), 747 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.59 ($CHCl_2$), 1.90-1.82

(2H, m, C*H*HC(OH)), 1.83 (1H, s, OH), 1.72-1.66 (2H, m, C*H*HCH), 1.64-1.56 (2H, m, CH*H*C(OH)), 1.44-1.34 (2H, m, CH*H*CH), 1.00-0.93 (1H, m, C*H*C(CH_3)$_3$), 0.88 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.0 ($CHCl_2$), 74.9 (C(OH)), 47.6 (*C*HC(CH_3)$_3$), 33.0 (*C*H_2C(OH)), 32.5 (*C*(CH_3)$_3$), 27.7 (C(*C*H_3)$_3$), 22.4 (*C*H_2CH); GC/MS (EI): 185.2, 187.2 [M-ClH_2O]$^+$, 167.1 [M-Cl_2]$^+$, 149.3 [M-Cl_2H_2O]$^+$; m.p = 60-61 °C.

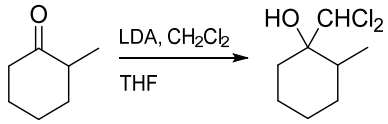
***trans*-4-(*tert*-Butyl)-1-(dichloromethyl)cyclohexan-1-ol 542i**



541i *trans*-**542i**

The compound was isolated from the same reaction mixture as above, to yield product as a white solid (61 mg, 26%) after column chromatography to separate the diastereoisomers (8:2 petroleum ether/Et_2O). ν (cm^{-1}); 3490 (br, O-H stretch), 2962 (C-H stretch), 1075 (C-O stretch), 755 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.08 (1H, s, $CHCl_2$), 2.28-2.18 (2H, m, C*H*HC(OH)), 1.80-1.73 (2H, m, C*H*HCH), 1.60-1.52 (2H, m, CH*H*C(OH)), 1.16-1.08 (1H, m, C*H*C(CH_3)$_3$), 1.04-0.94 (2H, m, CH*H*CH), 0.87 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.9 ($CHCl_2$), 74.8 (C(OH)), 47.2 (*C*HC(CH_3)$_3$), 36.0 (*C*H_2C(OH)), 32.4 (*C*(CH_3)$_3$), 27.8 (C(*C*H_3)$_3$), 23.7 (*C*H_2CH); GC/MS (EI): 185.2, 187.2 [M-ClH_2O]$^+$, 167.1 [M-Cl_2]$^+$, 149.3 [M-Cl_2H_2O]$^+$; m.p = 97-98 °C.

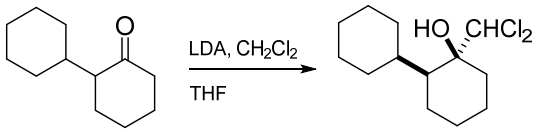
1-(Dichloromethyl)-2-methylcyclohexan-1-ol 542j



541j **542j**

The compound was prepared according to General Procedure 4 (using 0.120 mL, 1.00 mmol 2-methylcyclohexanone **541j**) to yield product as a white solid (0.139 g, 71%, inseparable 5.8:1 mixture of diastereoisomers) after column chromatography (9:1 petroleum ether/Et_2O). ν (cm^{-1}); 3475 (br, O-H stretch), 2934 (C-H stretch), 1146 (C-O stretch), 737 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ *major diastereoisomer*: 5.91 (1H, s, $CHCl_2$), 2.00-1.86 (2H, m, C*H*HC(OH) and C*H*CH_3), 1.76-1.19 (7H, m, CH*H*C(OH) and CH_2), 0.90 (3H, d, *J* 7, CHC*H*$_3$); *minor diastereoisomer*: 5.72 (1H, s, $CHCl_2$), 2.15-2.09 (1H, m, C*H*CH_3), 2.00-1.86 (1H, m, C*H*HC(OH)), 1.76-1.19 (7H, m, CH*H*C(OH) and CH_2), 0.90 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ *major diastereoisomer*: 79.8 ($CHCl_2$), 76.6 (C(OH)), 35.9 (*C*HCH_3), 30.7, 29.2, 25.6, 20.9 (CH_2), 14.2 (CH*C*H_3); *minor diastereoisomer*: 81.7 ($CHCl_2$), 76.6 (C(OH)), 35.6 (*C*HCH_3), 29.6, 28.9, 21.5, 19.2 (CH_2), 14.7 (CH*C*H_3); GC/MS (EI): 161.2, 163.1 [M-Cl]$^+$, 143.1, 145.1 [M-ClH_2O]$^+$, 126.1 [M-Cl_2]$^+$.

***cis*-2-(Dichloromethyl)-[1,1'-bi(cyclohexan)]-2-ol 542k**

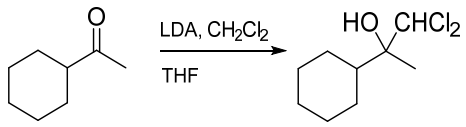


541k ***cis*-542k**

The compound was prepared according to General Procedure 4 (using 0.190 mL, 1.00 mmol 2-cyclohexylcyclohexanone **541k**) to yield product as a colourless oil (145 mg, 55%) after column chromatography to separate the 11:1 mixture of diastereoisomers (40:1 petroleum ether/Et_2O). ν (cm^{-1}); 3577 (br, O-H stretch), 2922 (C-H stretch), 1139

(C-O stretch), 788 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.09 (1H, s, $CHCl_2$), 1.97-1.84 (2H, m, C*H*$_2$C(OH)), 1.82-0.94 (18H, m, CH_2 and CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.5 ($CHCl_2$), 78.7 (C(OH)), 46.9 (*C*HC(OH)), 37.0 (*C*HCHC(OH)), 33.1 (CH_2), 30.7 (*C*H_2C(OH)), 28.8, 27.5, 27.0, 26.6, 26.4, 22.7, 21.2 (CH_2); GC/MS (EI): 211.2, 213.0 $[M\text{-}ClH_2O]^+$, 176.4 $[M\text{-}Cl_2H_2O]^+$. Data shown is for the major *cis*-diastereoisomer only, the minor *trans* diastereoisomer could not be isolated cleanly.

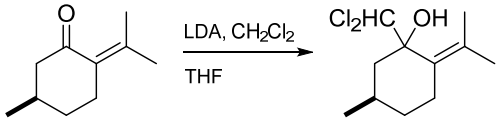
1,1-Dichloro-2-cyclohexylpropan-2-ol 542l



541l **542l**

The compound was prepared according to General Procedure 4 (using 0.140 mL, 1.00 mmol 1-cyclohexylethan-1-one **541l**) to yield product as a colourless oil (0.166 g, 79%) after column chromatography (9:1 petroleum ether/Et_2O). ν (cm^{-1}); 3468 (br, O-H stretch), 2929 (C-H stretch), 1067 (C-O stretch), 757 (C-Cl stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85 ($CHCl_2$), 1.93 (1H, s, OH), 1.88-1.74 (4H, m, CH and CH_2), 1.73-1.64 (2H, m, CH_2), 1.32 (3H, s, CH_3), 1.30-1.07 (5H, m, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.3 ($CHCl_2$), 77.9 (C(OH)), 44.2 (*C*HC(OH)), 27.5, 26.6, 26.5, 26.4 (CH_2), 19.5 (CH_3), one carbon missing due to overlapping peaks; GC/MS (EI): 211.2, 213.1 $[M+H]^+$, 192.0, 194.1 $[M\text{-}H_2O]^+$, 157.2, 159.2 $[M\text{-}ClH_2O]^+$.

(5*R*)-1-(Dichloromethyl)-5-methyl-2-(propan-2-ylidene)cyclohexan-1-ol 542n

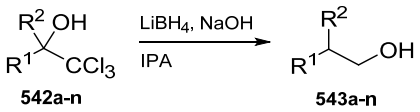


541n **542n**

The compound was prepared according to General Procedure 4 (using 0.160 mL, 1.00 mmol (*R*)-pulegone **541n**) to yield product as a yellow oil (0.162 g, 69%) after column

chromatography to separate the 13.3:1 mixture of diastereoisomers (95:5 petroleum ether/Et_2O). ν (cm^{-1}); 3569 (br, O-H stretch), 2952 (C-H stretch), 777 (C-Cl stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.22 (1H, s, $CHCl_2$), 2.82-2.74 (1H, m, C*H*HCH_2), 2.29 (1H, s, OH), 2.19-2.13 (1H, m, C*H*HC(OH)), 2.08 (3H, s, C=C(CH_3)), 1.78-1.71 (1H, m, C*H*HCHCH_3), 1.74 (3H, s, C=C(CH_3)), 1.70-1.57 (2H, m, C*H*CH_3, CH*H*CH_2), 1.35 (1H, t, *J* 13, CH*H*C(OH)), 0.99-0.88 (1H, m, CH*H*CHCH_3), 0.92 (3H, d, *J* 6.5, C*H*$_3$CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 130.3 (C=*C*(CH_3)$_2$), 128.3 (*C*=C(CH_3)$_2$), 81.2 (C(OH)), 79.7 ($CHCl_2$), 47.6 (*C*H_2C(OH)), 35.0 (*C*H_2CHCH_3), 30.0 (*C*HCH_3), 29.0 (*C*$H_2$$CH_2$CH), 24.3, 22.6 (C=C(*C*$H_3$)$_2$), 22.1 (CH*C*$H_3$); GC/MS (EI): 236.4 $[M]^+$, 165.2 $[M\text{-}Cl_2]^+$. Data shown is for the major diastereoisomer only, the minor diastereoisomer could not be isolated cleanly. The configuration of the C-1 centre is not known.

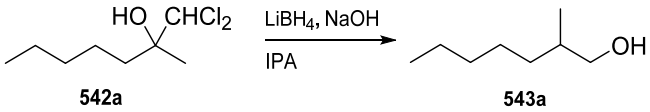
Jocic Reaction: General Procedure 5



542a-n **543a-n**

To a solution of dichloromethylcarbinol (1.00 equiv.) in dry propan-2-ol (4 mL/mmol substrate) was added $LiBH_4$ (4.00 equiv.) and NaOH (3.00 equiv.) under nitrogen, and stirred for 16 hours at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) and brine was added. The product was extracted with EtOAc (5 x 10 mL), the combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc).

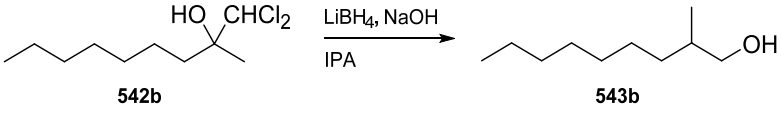
2-Methylheptan-1-ol 543a



542a **543a**

The compound was prepared according to General Procedure 5 (using 0.109 g, 0.548 mmol 1,1-dichloro-2-methylheptan-2-ol **542a**) to yield product as a colourless oil (21 mg, 30%) after column chromatography (7:3 petroleum ether/Et_2O). ν (cm^{-1}); 3347 (br, O-H stretch), 2925 (C-H stretch), 1032 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.54-3.39 (2H, m, C*H*$_2$OH), 1.65-1.55 (1H, m, C*H*CH_3), 1.44-1.21 (7H, m, C*H*HCHCH$_3$ and CH_2), 1.15-1.05 (1H, m, CH*H*CHCH$_3$), 0.91 (3H, d, *J* 6.5, CHC*H*$_3$), 0.89 (3H, t, *J* 7, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.6 (CH_2OH), 35.9 (*C*HCH_3), 33.2 (*C*H$_2$CHCH$_3$), 32.3, 26.8, 22.8 (CH_2), 16.8 (CH*C*H$_3$), 14.2 (*C*H$_3$CH$_2$); GC/MS (EI): 111.7 $[M-H_2O]^+$, 97.1 $[C_7H_{14}]^+$, 83.1 $[C_6H_{12}]^+$, 69.2 $[C_5H_{10}]^+$. Spectroscopic data are consistent with that previously reported.[475]

2-Methylnonan-1-ol 543b

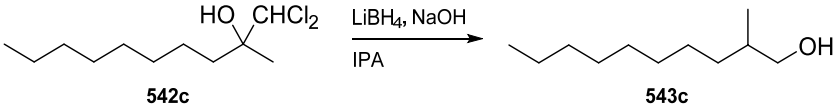


542b **543b**

The compound was prepared according to General Procedure 5 (using 0.148 g, 0.655 mmol 1,1-dichloro-2-methylnonan-2-ol **542b**) to yield product as a colourless oil (72.0 mg, 75%) after column chromatography (7:3 petroleum ether/Et_2O). ν (cm^{-1}); 3315 (br, O-H stretch), 2922 (C-H stretch), 1036 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.51 (1H, dd, *J* 10.5, 5.5, C*H*HOH), 3.42 (1H, dd, *J* 10.5, 6.5, CH*H*OH), 1.65-1.51 (1H, m, C*H*CH_3), 1.53-1.43 (11H, m, C*H*HCHCH$_3$ and CH_2), 1.15-1.03 (1H, m, CH*H*CHCH$_3$), 0.91 (3H, d, *J* 6.5, CHC*H*$_3$), 0.88 (3H, t, *J* 6.5, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.6 (CH_2OH), 35.9 (*C*HCH_3), 33.3 (*C*H$_2$CHCH$_3$), 32.0, 30.1,

29.5, 27.2, 22.8 (CH_2), 16.7 (CH*C*H_3), 14.3 (*C*H_3CH_2); GC/MS (EI): 158.2 $[M]^+$, 140.2 $[M\text{-}H_2O]^+$. Spectroscopic data are consistent with that previously reported.[489]

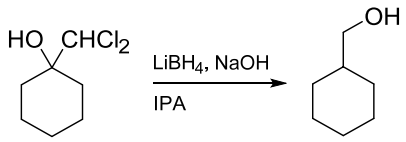
2-Methyldecan-1-ol 543c



542c **543c**

The compound was prepared according to General Procedure 5 (using 0.121 g, 0.502 mmol 1,1-dichloro-2-methyldecan-2-ol **542c**) to yield product as a colourless oil (58.0 mg, 66%) after column chromatography (7:3 petroleum ether/Et_2O). ν (cm^{-1}); 3328 (br, O-H stretch), 2921 (C-H stretch), 1036 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.51 (1H, dd, *J* 10.5, 6, C*H*HOH), 3.41 (1H, dd, *J* 10.5, 6.5, CH*H*OH), 1.65-1.54 (1H, m, C*H*CH_3), 1.43-1.15 (13H, m, C*H*HCHCH_3 and CH_2), 1.14-1.05 (1H, m, CH*H*CHCH_3), 0.91 (3H, d, *J* 6.5, CHC*H*$_3$), 0.88 (3H, t, *J* 6.5, C*H*$_3CH_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.6 (CH_2OH), 35.9 (*C*HCH_3), 33.3 (*C*H_2CHCH_3), 32.0, 30.1, 29.8, 29.5, 27.1, 22.8 (CH_2), 16.7 (CH*C*H_3), 14.3 (*C*H_3CH_2); GC/MS (EI): 154.3 $[M\text{-}H_2O]^+$, 125.0 $[C_9H_{18}]^+$, 112.0 $[C_8H_{16}]^+$, 98.0 $[C_7H_{14}]^+$. Spectroscopic data are consistent with that previously reported.[490]

Cyclohexylmethanol 543e

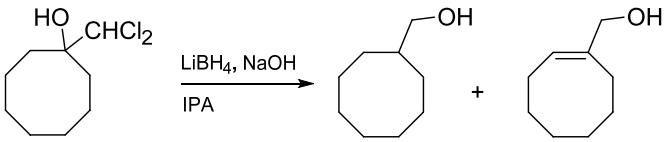


542e **543e**

The compound was prepared according to General Procedure 5 (using 98.0 mg, 0.536 mmol 1-(dichloromethyl)cyclohexan-1-ol **542e**) to yield product as a colourless oil (19.0 mg, 31%) after column chromatography (6:4 petroleum ether/Et_2O). ν (cm^{-1}); 3330 (br, O-H stretch), 2919 (C-H stretch), 1023 (C-O stretch); ^1H NMR ($CDCl_3$, 500

MHz) δ 3.44 (2H, d, *J* 6.5, C*H*$_2$OH), 1.79-1.71 (4H, m, C*H*HCHCH$_2$OH and C*H*HCH$_2$CH), 1.70-1.64 (1H, m, C*H*HCH$_2$CH$_2$), 1.53-1.42 (1H, m, C*H*CH$_2$OH), 1.31-1.11 (3H, m, CH*H*CH$_2$CH and CH*H*CH$_2$CH$_2$), 0.98-0.88 (2H, m, CH*H*CHCH$_2$OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 69.0 (CH_2OH), 40.6 (CH), 30.0 (*C*H$_2$CH), 26.7 (*C*H$_2$CH$_2$CH$_2$CH$_2$CH), 26.0 (*C*H$_2$CH$_2$CH$_2$CH); GC/MS (EI): 96.1 $[M\text{-}H_2O]^+$, 83.2 $[C_6H_{11}]^+$. Spectroscopic data are consistent with that previously reported.[491]

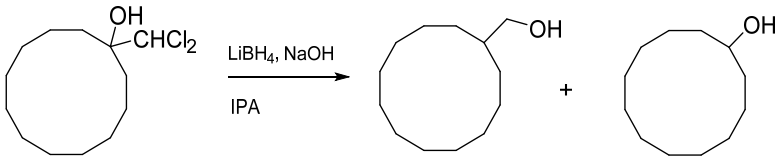
Cyclooctylmethanol 543f



542f **543f** **548**

The reaction was carried out according to General Procedure 5 (using 0.103 g, 0.489 mmol 1-(dichloromethyl)cyclooctan-1-ol **524f**) to yield a mixture of **543f** and **548** as a colourless oil (63.0 mg). Peaks at 5.68-5.55 ppm (1H, m, C*H*=CH$_2$), 4.04 ppm (2H, s, C*H*$_2$OH) and 2.24-2.02 ppm (4H, m, allylic) in the crude ^{1}H NMR spectrum suggest the presence of **548** by comparison to the literature.[492]

Cyclododecylmethanol 543g

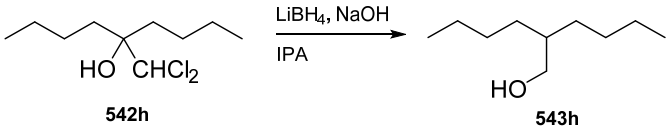


542g **543g** **544g**

The reaction was carried out according to General Procedure 5 (using 0.138 g, 0.517 mmol 1-(dichloromethyl)cyclododecan-1-ol **542g**) to yield a crude mixture as a colourless oil (90.0 mg, 88%). Integration of the relevant peaks at 3.90-3.79 ppm[485] (1H, m, **544**-C*H*OH) and 3.49 ppm[486] (2H, d, *J* 6, **543**-C*H*$_2$OH) provided a ratio of **543**:**544** = 96:4. Compound **543g** could be isolated as a colourless oil (57.6 mg, 56%)

after column chromatography (7:3 petroleum ether/Et_2O), and was fully characterised previously.

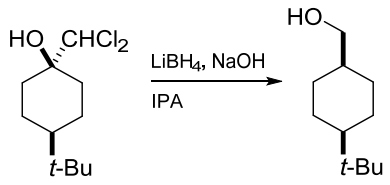
2-Butylhexan-1-ol 543 h



542h **543h**

The compound was prepared according to General Procedure 5 (using 0.111 g, 0.491 mmol 5-(dichloromethyl)decan-5-ol **542h**) to yield product as a colourless oil (50.0 mg, 65%) after column chromatography (7:3 petroleum ether/Et_2O). ν (cm^{-1}); 3328 (br, O-H stretch), 2924 (C-H stretch), 1043 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.54 (2H, d, *J* 5.5, C*H*$_2$OH), 1.49-1.41 (1H, m, C*H*CH_2OH), 1.38-1.22 (12H, m, CH_2), 1.18 (1H, br s, OH), 0.90 (6H, t, *J* 6.5, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 65.9 (CH_2OH), 40.7 (*C*HCH_2OH), 30.8, 29.3, 23.3 (CH_2), 14.2 (CH_3); GC/MS (EI): 158.0 M^+, 140.2 $[M\text{-}H_2O]^+$, 112.1 $[C_8H_{16}]^+$, 98.0 $[C_7H_{14}]^+$. Spectroscopic data are consistent with that previously reported.[480]

***cis*-4-(*tert*-Butyl)cyclohexyl)methanol 543i**

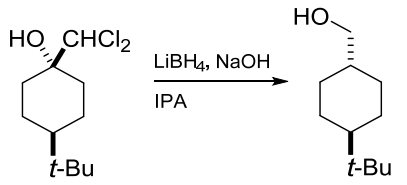


cis-**542i** *cis*-**543i**

The compound was prepared according to General Procedure 4 (using 0.150 g, 0.628 mmol *cis*-4-(*tert*-butyl)-1-(dichloromethyl)cyclohexan-1-ol **542i**) to yield product as a white solid (61.0 mg, 26%) after column chromatography (8:2 petroleum ether/Et_2O). ν (cm^{-1}); 3248 (br, O-H stretch), 2932 (C-H stretch), 1031 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.67-3.61 (2H, m, C*H*$_2$OH), 1.87-1.76 (3H, m, C*H*CH_2OH and C*H*$HCHCH_2OH$), 1.57-1.51 (2H, m, C*H*$HCHC(CH_3)_3$), 1.50-1.41

(2H, m, CH*H*CHCH$_2$OH), 1.19-1.15 (1H, m, OH), 1.10-0.94 (3H, m, C*H*C(CH$_3$)$_3$ and CH*H*CHC(CH$_3$)$_3$), 0.83 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 63.9 (CH$_2$OH), 48.5 (*C*HC(CH$_3$)$_3$), 35.5 (*C*HCH$_2$OH), 32.7 (*C*(CH$_3$)$_3$), 27.60 (C(*C*H$_3$)$_3$), 27.59 (*C*H$_2$CHCH$_2$OH), 22.2 (*C*H$_2$CHC(CH$_3$)$_3$); GC/MS (EI): 170.3 [M]$^+$; m.p = 62-63 °C. Spectroscopic data are consistent with that previously reported.[461, 462]

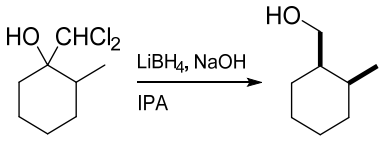
***trans*-4-(*tert*-Butyl)cyclohexyl)methanol 543i**



trans-**542i** *trans*-**543i**

The compound was prepared according to General Procedure 4 (using 94.0 mg, 0.393 mmol *trans*-4-(*tert*-butyl)-1-(dichloromethyl)cyclohexan-1-ol **542i**) to yield product as a colourless oil (19.0 mg, 29%) after column chromatography (6:4 petroleum ether/Et$_2$O). ν (cm^{-1}); 3324 (br, O-H stretch), 2938 (C-H stretch), 1033 (C-O stretch); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.44 (2H, d, *J* 6.5, C*H*$_2$OH), 1.87-1.76 (4H, m, CH$_2$), 1.45-1.27 (1H, m, C*H*CH$_2$OH), 1.27 (1H, br s, OH), 1.04-0.88 (5H, m, CH$_2$ and C*H*C(CH$_3$)$_3$), 0.84 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 67.0 (CH$_2$OH), 48.4 (*C*HC(CH$_3$)$_3$), 40.7 (*C*HCH$_2$OH), 32.4 (*C*(CH$_3$)$_3$), 30.1 (CH$_2$), 27.7 (C(*C*H$_3$)$_3$), 26.9 (CH$_2$); GC/MS (EI): 152.1 [M-H$_2$O]$^+$, 113.1 [C$_7$H$_{13}$]$^+$. Spectroscopic data are consistent with that previously reported.[461, 462]

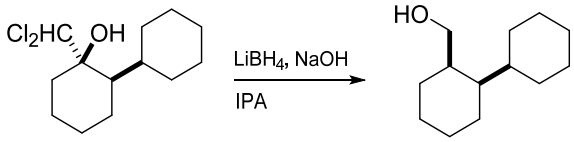
(±)-*cis*-2-Methylcyclohexyl)methanol 543j



542j *cis*-**543j**

The compound was prepared according to General Procedure 4 (using 93.6 mg, 0.475 mmol 1-(dichloromethyl)-2-methylcyclohexan-1-ol **542j**, 5.8:1 ratio of diastereoisomers) to yield product as a colourless oil (36.0 mg, 59%) after column chromatography to separate the 33:1 ratio of diastereoisomers (1:1 petroleum ether/Et_2O). ν (cm^{-1}); 3313 (br, O-H stretch), 2920 (C-H stretch), 1030 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.57-3.44 (2H, m, C*H*$_2$OH), 2.00-1.91 (1H, m, C*H*CH_3), 1.73-1.66 (1H, m, C*H*CH_2OH), 1.65-1.12 (8H, m, CH_2), 0.86 (3H, d, *J* 7, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 65.3 (CH_2OH), 42.9 (*C*HCH_3), 32.8 (CH_2), 30.0 (*C*HCH_2OH), 25.1, 24.5, 22.0 (CH_2), 13.9 (CH_3); GC/MS (EI): 128.2 $[M]^+$, 110.1 $[M-H_2O]^+$, 97.2 $[C_7H_{13}]^+$, 82.2 $[C_6H_{10}]^+$. This compound was previously reported in the literature without ^1H or ^{13}C NMR data.[493]

(±)-*cis*-[1,1'-bi(Cyclohexan)]-2-yl)methanol 543k

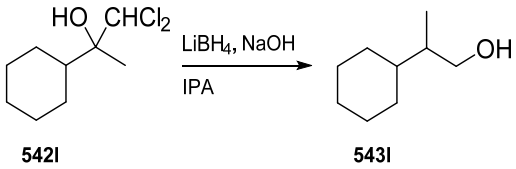


cis-**542k** *cis*-**543k**

The compound was prepared according to General Procedure 4 (using 0.145 g, 0.547 mmol *cis*-2-(dichloromethyl)-[1,1'-bi(cyclohexan)]-2-ol **542k**) to yield product as a white solid (42.0 mg, 39%) after column chromatography (7:3 petroleum ether/Et_2O). ν (cm^{-1}); 3322 (br, O-H stretch), 2915 (C-H stretch), 1027 (C-O stretch); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76-3.69 (2H, m, C*H*$_2$OH), 2.08-2.00 (1H, m, C*H*CH_2OH), 1.99-0.70 (20H, m, CH_2 and CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.9 (CH_2OH), 45.4

(CH), 39.2 (CH), 37.4 (*C*HCH$_2$OH), 31.6, 30.8, 27.6, 27.0, 26.8, 26.65, 26.63, 25.5, 20.8 (CH$_2$); GC/MS (EI): 178.2 [M-H$_2$O]$^+$, 165.2 [C$_{12}$H$_{22}$]$^+$; m.p = 56-57 °C. This compound was previously reported without ^{1}H or ^{13}C NMR data.[463]

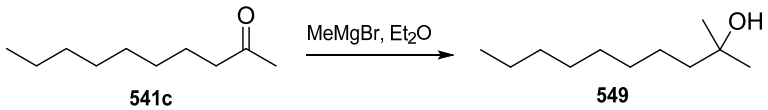
2-Cyclohexylpropan-1-ol 543l



542l **543l**

The compound was prepared according to General Procedure 4 (using 96.0 mg, 0.455 mmol 1,1-dichloro-2-cyclohexylpropan-2-ol **542l**) to yield product as a colourless oil (30.0 mg, 46%) after column chromatography (7:3 petroleum ether/Et$_2$O). ν (cm^{-1}); 3345 (br, O-H stretch), 2921 (C-H stretch), 1018 (C-O stretch); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.65-3.58 (1H, m, C*H*HOH), 3.50-3.43 (1H, m, CH*H*OH), 1.78-1.60 (5H, m, CH$_2$), 1.54-1.44 (1H, m, C*H*CH$_3$), 1.38-1.29 (1H, m, C*H*CHCH$_3$), 1.27-0.93 (5H, m, CH$_2$), 0.89 (3H, d, *J* 7, CHC*H*$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 66.5 (CH$_2$OH), 41.1 (*C*HCH$_2$OH), 39.5 (*C*HCHCH$_3$), 31.1, 29.0, 26.90, 26.85, 26.80 (CH$_2$), 13.5 (CH$_3$); GC/MS (EI): 124.3 [M-H$_2$O]$^+$. Spectroscopic data are consistent with that previously reported.[494]

2-Methylnonan-2-ol 549

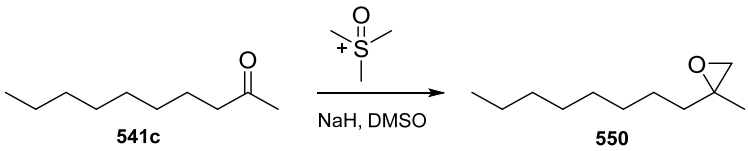


541c **549**

To a solution of 2-decanone **541c** (0.380 mL, 2.00 mmol) in dry Et$_2$O (5 mL) was added methylmagnesium bromide (2.00 mL, 3M in THF, 6.00 mmol) dropwise, at 0 °C. The mixture was heated at reflux temperature for two hours, then cooled to 0 °C and quenched with saturated NH$_4$Cl (aq.). The mixture was extracted with Et$_2$O, washed with water, dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The

compound was a colourless oil (0.309 g, 90%) and was used without further purification. ν (cm^{-1}); 3361 (br, O-H stretch), 2925 (C-H stretch), 1150 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48-1.43 (2H, m, C*H*$_2$C(OH)), 1.37-1.23 (12H, m, CH_2), 1.21 (6H, s, (C*H*$_3$)$_2$C(OH)), 0.88 (3H, t, *J* 6.5, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 71.2 (C(OH)), 44.2 (*C*H$_2$C(OH)), 32.0, 30.3, 29.8, 29.4 (CH_2), 29.3 ((*C*H$_3$)$_2$C(OH)), 24.5, 22.8 (CH_2), 14.3 (*C*H$_3$CH$_2$); GC/MS (EI): 173.1 $[M+H]^+$, 157.1 $[C_{10}H_{21}O]^+$, 153.9 $[M-H_2O]^+$. Spectroscopic data are consistent with that previously reported.[495]

2-Heptyl-2-methyloxirane 550

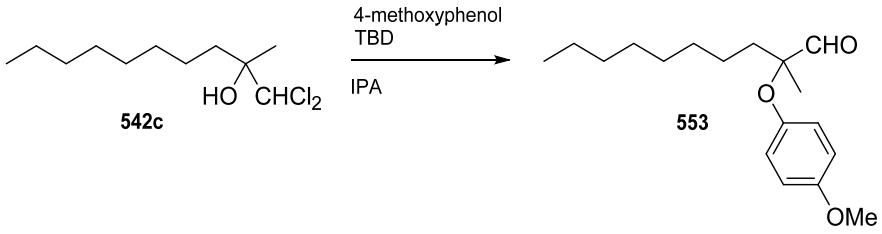


541c **550**

A round-bottomed flask was charged with NaH (60% dispersion in mineral oil, 0.40 g, 10 mmol), and the NaH was washed with petroleum ether. Trimethylsulfoxonium iodide (2.2 g, 10 mmol) was then added, followed by DMSO (5 mL), at 0 °C. The mixture was stirred for 20 minutes at room temperature, then a solution of 2-decanone **541c** (0.95 mL, 5.0 mmol) in DMSO (5 mL) was added. The reaction was stirred at room temperature for a further 22 hours then cooled to 0 °C and water was added. The mixture was extracted with 1:1 petroleum ether/Et_2O, the combined organic fractions were washed with water and brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The compound was a colourless oil (0.62 g, 73%) and was used without further purification. ν (cm^{-1}); 2923 (C-H stretch), 901, 798 (C-O stretch); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.60 (1H, d, *J* 5, C*H*HO), 2.57 (1H, d, *J* 5, CH*H*O), 1.62-1.55 (1H, m, C*H*HC(O)), 1.51-1.44 (1H, m, CH*H*C(O)), 1.42-1.34 (2H, m, C*H*$_2$CH$_2$C(O)), 1.32-1.19 (10H, m, CH_2), 1.30 (3H, s, CH_3C(O)), 0.88 (3H, t, *J* 6.5, C*H*$_3$CH$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 57.2 (CO), 54.1 (CH_2O), 36.9 (*C*H$_2$C(O)), 32.0, 29.8, 29.7, 29.4

(CH_2), 25.4 ($CH_2CH_2C(O)$), 22.8 (CH_2), 21.0 ($CH_3C(O)$), 14.2 (CH_3CH_2); GC/MS (EI): 170.2 $[M]^+$. Spectroscopic data are consistent with that previously reported.[496]

2-(4-Methoxyphenoxy)-2-methyldecanal 553



To a solution of 1,1-dichloro-2-methyldecan-2-ol **542c** (0.241 g, 1.00 mmol) and 4-methoxyphenol (0.472 g, 3.00 mmol) in dry 2-propanol (4 mL) was added TBD (1.12 g, 8.00 mmol), and the reaction was stirred at room temperature for 15 hours. Saturated NH_4Cl (aq.) was added and the mixture was extracted with EtOAc. The combined organic fractions were washed with pH 2 buffer and water, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography (95:5 to 8:2 petroleum ether/EtOAc) to yield product as a colourless oil (0.147 g, 50%). ν (cm^{-1}); 2924 (C-H stretch), 1734 (C=O stretch), 1505 (C=C stretch), 1214 (C-O stretch), 841 (Ar-H bend); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.85 (1H, s, CHO), 6.84-6.76 (4H, m, Ph-H), 3.77 (3H, s, CH_3O), 1.83-1.75 (1H, m, C*H*HC(CHO)), 1.73-1.65 (1H, m, CH*H*C(CHO)), 1.48-1.34 (2H, m, $CH_2CH_2C(CHO)$), 1.33-1.20 (10H, m, CH_2), 1.27 (3H, s, C*H*$_3$C(CHO)), 0.88 (3H, t, *J* 6.5, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.4 (CHO), 155.7 (Ar-C_{para}), 148.7 (Ar-C_{ipso}), 122.1, 114.6 (Ar-C), 85.9 (*C*(CHO)), 55.7 (CH_3O), 36.4 ($CH_2C(CHO)$), 32.0, 30.1, 29.5, 29.3 (CH_2), 23.0 ($CH_2CH_2C(CHO)$), 22.8 (CH_2), 18.7 ($CH_3C(CHO)$), 14.2 (CH_3CH_2); HRMS (ESI) *m*/*z*: calcd. for $C_{18}H_{28}NaO_3$ $[M+Na]^+$ 315.1931, found 315.1927.

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